A Dissertation on

PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

COIMBATORE

APRIL 2015

CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr. SURESH.S*** *and submitted in partial fulfillment of the requirements for the Degree of* ***M.D.,General Medicine****, Branch I of* ***The Tamilnadu Dr. M.G.R. Medical University, Chennai.***

Date: **Guide, Professor & Chief,**

Medical Unit II.

Date: **Professor & Head,**

Department of Medicine.

Date: **Dean,**

Coimbatore Medical College,

Coimbatore.

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : S. SURESH

Course : M.D GENERAL MEDICINE

Period of Study : 2012 - 2015

College : COIMBATORE MEDICAL COLLEGE

Dissertation Topic : PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION.

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not accepted~~ and you are permitted / ~~Not permitted~~ to proceed with the above Study.

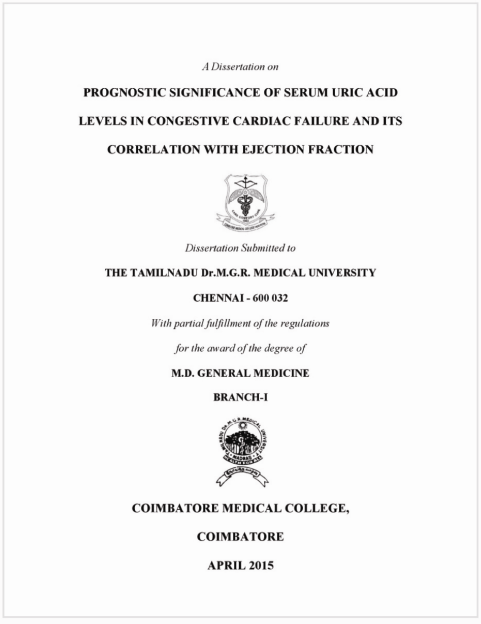
DEAN
Coimbatore Medical College & Hospital,
Coimbatore

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201211319.md General Medicine SU…
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	PROGNOSTIC SIGNIFICANCE OF S.
File name:	suresh_thesis_copy.docx
File size:	3.76M
Page count:	110
Word count:	14,690
Character count:	87,000
Submission date:	14-Sep-2014 12:50PM
Submission ID:	449251942



A Dissertation on

PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

COIMBATORE

APRIL 2015

DECLARATION

I solemnly declare that the dissertation titled "**PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION**" was done by me from AUGUST 2013 to JULY 2014 under the guidance and supervision of Professor. Dr. S.MANOHARAN. M.D.,

This dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

Place: Coimbatore Dr. SURESH. S

Date:

ACKNOWLEDGEMENT

I wish to express my sincere thanks to our respected Dean **Dr. S. REVWATHY. M.D., DGO., DNB.,** for having allowed me to conduct this study in our hospital.

I express my heartfelt thanks and deep gratitude to the Head of the Department of Medicine, Prof. **Dr. KUMAR NATARAJAN. M.D.,** and my guide **Prof. Dr. S. MANOHARAN. M.D.,** for his generous help and guidance in the course of the study.

I am extremely grateful to Prof. **Dr. Isaac Christian Moses. M.D**., and **Dr. Chakkravarthy.M.D., D.N.B.,** for his valuable help and cooperation and allowing me to use institutional facilities.

I sincerely thank all Professors and Asst. Professors- **Dr.K.Ganesamoorthy. M.D., Dr.K.Jamunarani. M.D., Dr.A.Akila. M.D., Dr.S.Ramkumar. M.D., and Dr.S Selvamani. M.D.,** for their guidance and kind help.

My sincere thanks to all my friends and post-graduate colleagues for their whole hearted support and companionship during my studies.

I thank all my **PATIENTS**, who formed the backbone of this study, without whom this study would not have been possible.

Place: **Dr. SURESH. S**

Date:

LIST OF ABBREVIATIONS USED

ABG	–	Arterial Blood Gas
ACCF	–	American College Of Cardiology Foundation
ACE	–	Angiotensin Converting Enzyme
ACS	–	Acute Coronary Syndrome
ADCHF	–	Acute Decompensated Chronic Heart Failure
ADHF	–	Acute Decompensated Heart Failure
AHA	–	American Heart Association
AHF	–	Acute Heart Failure
AHFS	–	Acute Heart Failure Syndromes
amido PRT	–	amido Phosphoribosyl Transferase
ATP	–	Adenosine Tri Phosphate
BNP	–	Brain Natriuretic Peptide
CAD	–	Coronary Artery Disease
CHF	–	Congestive Heart Failure
CVD	–	Coronary Vascular Disease
DNA	–	Deoxyribo Nucleic Acid
ECG	–	Electrocardiography
EF	–	Ejection Fraction
eNO	–	endothelial Nitric Oxide

GFR	–	Glomerular Filtration Rate
GMP	–	Guanosine Mono Phosphate
HF	–	Heart Failure
HFpEF	–	Heart failure with preserved ejection fraction
HFrEF	–	Heart failure with reduced ejection fraction
HPRT	–	Hypoxanthine Phosphoribosyl Transferase
hsCRP	–	highly sensitive C Reactive Protein
hURAT	–	human Uric Acid Transporter
ICU	–	Intensive Care Unit
IMP	–	Inosine Mono Phosphate
JVP	–	Jugular Venous Pressure
LVEF	–	Left Ventricular Ejection Fraction
NCEP- ATP- III	–	National Cholesterol Educational Program- Adult Treatment Panel III
NOS 1	–	Nitric Oxide Synthase 1
NT-proBNP	–	N-terminal pro-Brain Natriuretic Peptide
NYHA	–	New York Heart Association
OAT	–	Organic Anion Transporter
PKC	–	Protein Kinase C
PRPP	–	Phospho Ribosyl Pyro Phosphate

RAAS	–	Renin Angiotensin Aldosterone System
RNA	–	Ribo Nucleic Acid
ROS	–	Reactive Oxygen Species
SBP	–	Systolic Blood Pressure
SOD	–	Superoxide Desmutase
T2DM	–	Type 2 Diabetes Mellitus
UA	–	Uric Acid
URAT1	–	Urate Transporter 1

CONTENTS

PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION

ABSTRACT

OBJECTIVE:

The aim of the study is to access the prognostic significance of serum uric acid levels in patients with congestive cardiac failure and its correlation with ejection fraction.

MATERIALS AND METHODS:

This study was performed in Department of Medicine, Coimbatore Medical College hospital, Coimbatore. Serum uric acid levels were measured in 100 heart failure patients and their levels were correlated with ejection fraction and NYHA functional class for heart failure. Hemodynamic characteristics and risk factors of the patients were also assessed. Patients were followed up for 30 days with end points of cardiac death or rehospitalisation.

RESULTS:

Out of 100 patients analysed, 73 patients had higher uric acid levels and 27 had normal uric acid levels. Serum uric acid levels correlated negatively with ejection fraction and positively with NYHA functional class, thus predicting the prognosis and severity in heart failure patients. Patients with higher uric acid levels were in severe heart failure and required significantly more rehospitalisation and had more deaths compared to those with normal uric acid levels.

CONCLUSION:

Higher serum uric acid levels is a prognostic predictor in patients with congestive cardiac failure. Monitoring of serum uric acid levels may be useful for the management of patients with congestive cardiac failure.

Key Words : Uric acid, Congestive cardiac failure, Ejection fraction, Prognosis.

INTRODUCTION

Congestive heart failure (CHF) is an important cause for morbidity and mortality irrespective of age and sex across the globe. The prevalence of heart failure has significantly increased over the past decade and it is the leading cause of hospitalization in developed and developing countries. This includes patients presenting with new onset heart failure and as well as with worsening of pre- existing chronic heart failure. Heart failure is associated with poor prognosis leading to frequent hospitalizations, poor quality of life and shortened life span. Hence it is important to identify simple and effective investigatory modalities for early diagnosis, risk stratification and prognosis.

Uric acid (UA) is a metabolic end product of purine metabolism. Uric acid, an important antioxidant in plasma acts as a free radical when in excess. Uric acid appears to play a pathological role in the development of hypertension, diabetes, obesity and metabolic syndrome contributing to cardiovascular mortality. Excess uric acid levels results in endothelial dysfunction, increased RAAS (Renin Angiotensin Aldosterone System) activation and vascular smooth muscle proliferation leading to cardiovascular and renal diseases.[1]

Serum uric acid levels are increased in CHF mostly by increased generation and partly by reduced excretion or both. Elevated uric acid levels

indicate cardiac dysfunction and progression of heart failure through oxidative stress and free radical injury by increased xanthine oxidase activity.[2]

Epidemiological studies have shown that increased uric acid levels serve as a valid prognostic marker in congestive heart failure and indicate metabolic, functional and hemodynamic derangements. The purpose of this study is to determine the association between uric acid levels and heart failure and to find its significance in predicting mortality and severity of the disease as a prognostic risk marker.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

Aim:

The aim of the study is to determine the prognostic significance of serum uric acid levels in patients with congestive cardiac failure and its correlation with ejection fraction.

Objectives:

1. To validate increase in serum uric acid levels in congestive heart failure.

2. To correlate serum uric acid levels with ejection fraction.

3. To establish the relationship of increased uric acid levels to functional class (NYHA New York Heart Association) in congestive heart failure in predicting the severity.

4. To determine the association of serum uric acid levels to the individual risk factors in patients with congestive heart failure.

5. To determine the prognosis in terms of 30 day mortality rate in congestive heart failure patients with high uric acid levels.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HEART FAILURE

Definition:

Heart failure (HF) is a complex clinical syndrome due to inherited or acquired abnormality of cardiac structural or functional impairment in ventricular filling or ejection of blood, resulting in a constellation of clinical symptoms and signs, frequent hospitalizations, a poor quality of life and a shortened life expectancy.[3]

Epidemiology:

Heart failure is a global problem affecting more than 20 million people.[5] The incidence and prevalence of heart failure has been on the increasing trend in the last 30 years due to increase in the lifespan.[4] The disease increases with age affecting 6-10% of people over the age of 65. Annually 0.5 to 1.8 million people are affected in India with estimated total prevalence of about 1.3 to 4.6 million.[6] The increasing prevalence of heart failure may be due to improved diagnostic and therapeutic techniques for common cardiac ailments.

Despite tremendous advancements in the management of heart failure over the past decade, the morbidity and mortality in patients with heart failure

remains on the higher side. In the western countries, heart failure is seen mostly in the elderly population. However, in India, the picture is quite different with relatively younger age group are affected more in comparison to western countries. Heart failure is usually associated with risk factors like diabetes mellitus, hypertension, ischaemic heart disease, obesity and valvular heart disease.[7,8] In India, the leading causes of heart failure are coronary artery disease, diabetes mellitus, hypertension, valvular heart disease and myocarditis. Compared to the western world, rheumatic heart disease is a more significant cause of heart failure in India.

Classification of Heart Failure:

Acute and chronic heart failure:

Acute heart failure is defined as the structural and functional maladaptation of the heart, occurring in a very short interval of time, leading to rapid onset of clinical signs and symptoms, requiring emergency lifesaving support.[9] It is characterized by sudden onset of severe symptoms requiring emergent treatment. The development of symptoms is usually preceded by a precipitating event. The precipitating factors may act on a previously normal heart in new onset Heart failure or in the already diseased heart, causing acute decompensation of chronic heart failure. The sudden shift of blood from the

systemic circulation to the pulmonary circulation can lead to sudden onset of dyspnoea in the absence of peripheral edema.

Chronic heart failure refers to a comparatively stable state characterized by persistent but frequently stable symptoms on and off, requiring indefinite treatment also known as compensated heart failure. The progression of this state to acute decompensation occurs following a triggering factor. The precipitating factor may vary in individual patients. Fatigue is a very common symptom due to under perfusion of the skeletal muscles resulting in exercise intolerance. Accumulation of fluid may occur, resulting in pulmonary and peripheral congestion and anasarca described as congestive heart failure. However, in some patients heart failure may present in the absence of these congestive symptoms. So the term ‘congestive heart failure’ has been replaced by the term ‘heart failure’.

Systolic and diastolic heart failure:

Systolic heart failure (the most common type) refers to a clinical syndrome characterized by impaired left ventricular contractility and decreased cardiac output. It presents with symptoms of fatigue, breathlessness and poor exercise tolerance. These patients are characterized by the presence of a large, dilated heart with significant systolic dysfunction.

Diastolic dysfunction refers to patients in whom the left ventricular ejection fraction is normal or near normal at rest with normal sized heart. The pathophysiology responsible for diastolic heart failure is usually impaired diastolic filling of the ventricles with normal contractility and cardiac output. It may be accompanied by left ventricular hypertrophy.

Left and right heart failure:

In the absence of regurgitation, abnormal communications or shunts, both the right heart and left heart function like a circuit in series, contributes almost equal cardiac output. Hence either side cannot eject more blood than the other. The term left heart failure is used in the context of congestion and increased pressures in the pulmonary circulation. Right heart failure is used in patients presenting with signs and symptoms of congestion and increased pressures in the systemic circulation, manifesting as elevated jugular venous pressure and congestive liver, ascites and dependant edema.

Current Classification:

In patients with heart failure, the left ventricular functional abnormalities are usually variable. They may have a wide spectrum of left ventricular size and function. Both systolic and diastolic dysfunction may be seen in many patients with heart failure, irrespective of the ejection fraction. The most

important factor in classifying patients with heart failure is the left ventricular ejection fraction, since the clinical features, risk factors, prognosis and response to therapy differs in patients with varying ejection fractions. Ejection fraction is an important determinant of left ventricular function and therefore heart failure patients are primarily classified into those with reduced ejection fraction and those with preserved ejection fraction. (Fig. 1)

Heart failure with reduced ejection fraction (HFrEF):

Majority of the patients with reduced ejection fraction have varying degrees of enlargement of the left ventricles and decreased cardiac output. The cut-off limit of ejection fraction for defining has varied from ≤35%, <40% and ≤40% over the past few years.[10-12] The current guidelines recommend an ejection fraction value of ≤40% for the diagnosis of reduced ejection fraction in the presence of signs and symptoms of heart failure commonly referred as systolic failure.[U]

Heart failure with preserved ejection fraction (HFpEF):

Around 50% percentage of patients with heart failure who do not have reduced ejection fraction,[13] but ventricle filling is impaired with normal or increased cardiac output. They are commonly referred as diastolic failure. Since some of the patients do not have an entirely normal ejection fraction, but also do

not have a significant systolic dysfunction, the term preserved ejection fraction has been coined.

Patients with an ejection fraction of 40% to 50% are referred to as an intermediate group. Making a diagnosis of heart failure with preserved ejection fraction is challenging, since majority of them are non-cardiac causes. These patients usually belong to the elderly age group with history of hypertension, diabetes mellitus, obesity, dyslipidemia and arrhythmias.[13,14]

The most common cause of heart failure with preserved ejection fraction is hypertension.[15] It has been found that some of the patients with preserved ejection fraction were previously classified under heart failure with reduced ejection fraction.[16] Further studies are required to further characterize these patients, because these patients have a distinct clinical profile when compared to those with persistent reduced or preserved ejection fraction. No definite therapies are available for patients with preserved ejection fraction.

	CLASSIFICATION	EF (%)	DESCRIPTION
I	Heart failure with reduced ejection fraction (HFrEF)	**≤40**	Also referred to as systolic HF. It is only in these patients that efficacious therapies have been demonstrated to date.
II	Heart failure with preserved ejection fraction (HFpEF)	**>50**	Also referred to as diastolic HF. To date, efficacious therapies have not been identified.
II a	HFpEF, borderline	**40-49**	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.
II b	HFpEF, improved	**>40**	It includes the subset of patients with HFpEF previously had HFrEF.

Fig.1. Classification of patients based on ejection fraction

Severity of Heart Failure:

The severity of heart failure can be assessed by classifying the patients. Two classification systems are accepted worldwide.

The first one is a functional classification, the New York Heart Association (NYHA) classification. (Fig. 2) It provides information about the functional capacity and the exercise tolerance of the patient. Patients are classified

into four classes. It is a very simple and easy method to estimate the cardiac function with symptoms alone.

NYHA CLASS	SYMPTOMS
CLASS I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain
CLASS II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
CLASS III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain
CLASS IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Fig 2. New York Heart Association (NYHA) classification of Heart Failure

The second staging is recommended by the American Heart Association (AHA) and American College of Cardiology Foundation (ACCF). (Fig. 3) It helps in assessing the development and progression of heart failure over a period of time. It analyses both the abnormalities in cardiac structure and the risk

factors associated with heart failure. There are numerous etiologies for heart failure. (Fig. 4)

AHA/ACCF STAGE	DESCRIPTION
STAGE A	At high risk for HF but without structural heart disease or symptoms of HF
STAGE B	Structural heart disease but without signs or symptoms of HF
STAGE C	Structural heart disease with prior or current symptoms of HF
STAGE D	Refractory HF requiring specialized interventions

Fig. 3. AHA/ACCF staging of Heart Failure

Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated cardiomyopathy
Myocardial infarction[a]	Familial/genetic disorders
Myocardial ischemia[a]	Infiltrative disorders[a]
Chronic pressure overload	Toxic/drug-induced damage
Hypertension[a]	Metabolic disorder[a]
Obstructive valvular disease[a]	Viral
Chronic volume overload	Chagas' disease
Regurgitant valvular disease	Disorders of rate and rhythm
Intracardiac (left-to-right) shunting	Chronic bradyarrhythmias
Extracardiac shunting	Chronic tachyarrhythmias
Preserved Ejection Fraction (>40–50%)	
Pathologic hypertrophy	Restrictive cardiomyopathy
Primary (hypertrophic cardiomyopathies)	Infiltrative disorders (amyloidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases (hemochromatosis)

Aging	Fibrosis
	Endomyocardial disorders
Pulmonary Heart Disease	
Cor pulmonale	
Pulmonary vascular disorders	
High-Output States	
Metabolic disorders	Excessive blood-flow requirements
Thyrotoxicosis	Systemic arteriovenous shunting
Nutritional disorders (beriberi)	Chronic anemia

Note: [a] Indicates conditions that can also lead to heart failure with a preserved ejection fraction.

Fig. 4. Etiologies of Heart Failure

ACUTE HEART FAILURE SYNDROMES:

Definition:

Acute heart failure syndromes (AHFS) is a broad term that encompasses a group of related disorders, which were previously known by various overlapping terms, including acute heart failure (AHF), acute decompensated heart failure (ADHF) and acute decompensation of chronic heart failure (ADCHF). AHFS is defined as new onset or recurrence of gradually or rapidly developing symptoms and signs of heart failure usually preceded by a precipitating factor, requiring urgent or emergent life saving therapy and resulting in hospitalization

Classification:

The wide spectrum of AHFS does not allow a comprehensive classification. A lot of classification schemes have been tried, but none of them have been accepted universally. A simple approach to classify AHFS relies on the presence of previous history of heart failure symptoms and signs.[9] Based on this, the patients can be simply classified into de novo (new onset) heart failure and worsening of chronic heart failure. (Fig. 5)

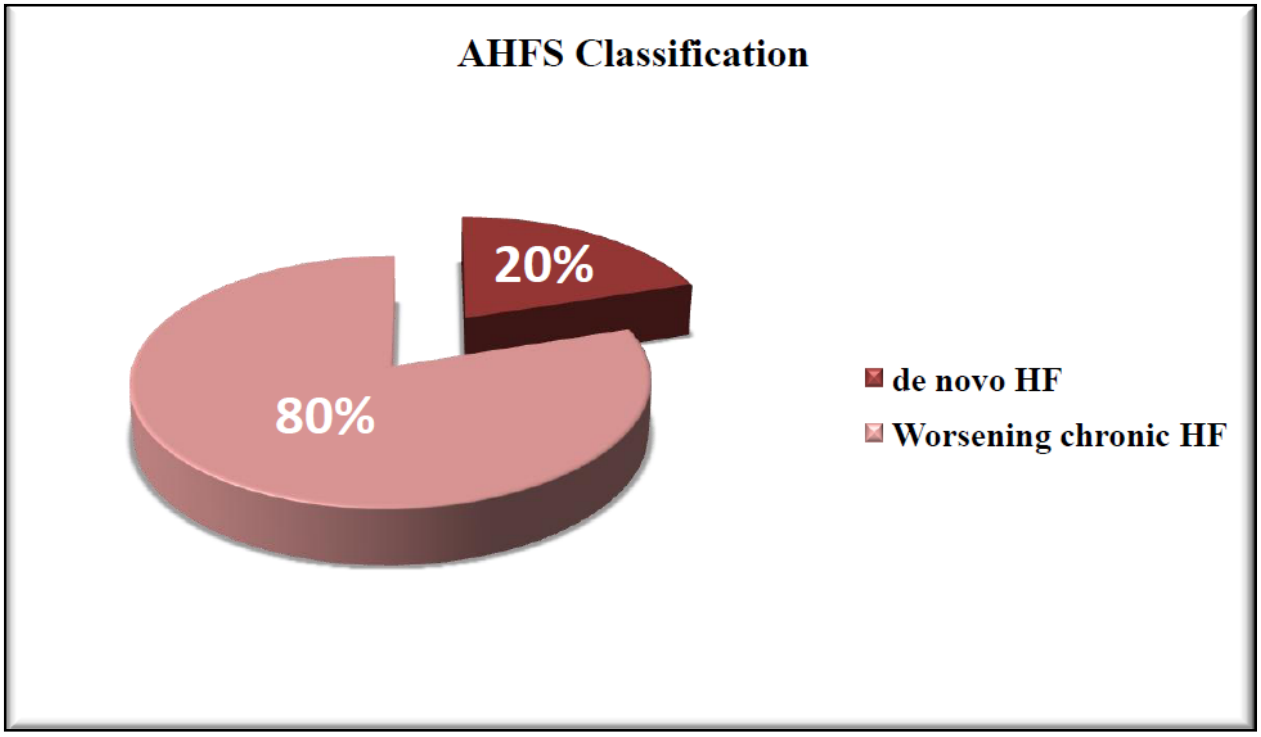


Fig. 5. Classification of Acute Heart Failure Syndromes

De Novo Heart Failure:

Patients in this category develop symptoms and signs of heart failure for the first time in their life, without previous history of heart disease. They may or may not have cardiovascular risk factors like diabetes, hypertension or dyslipidemia. Acute myocarditis is an example for de novo AHFS without any prior risk factor. More often patients will have risk factors for heart disease with prior subtle symptoms like fatigue.

Worsening chronic heart failure:

Majority (80%) of the patients with AHFS belong to this category. They have history of heart failure on a long term basis and present with symptoms of acute decompensation by a triggering factor. Some of the patients in this group suffer from advanced heart failure, refractory to available modalities of treatment, requiring cardiac transplantation.

Causes and Precipitating Factors:

Patients with AHFS most often present with symptoms due to a precipitating factor. The various causes and precipitating factors are mentioned in Fig. 6.

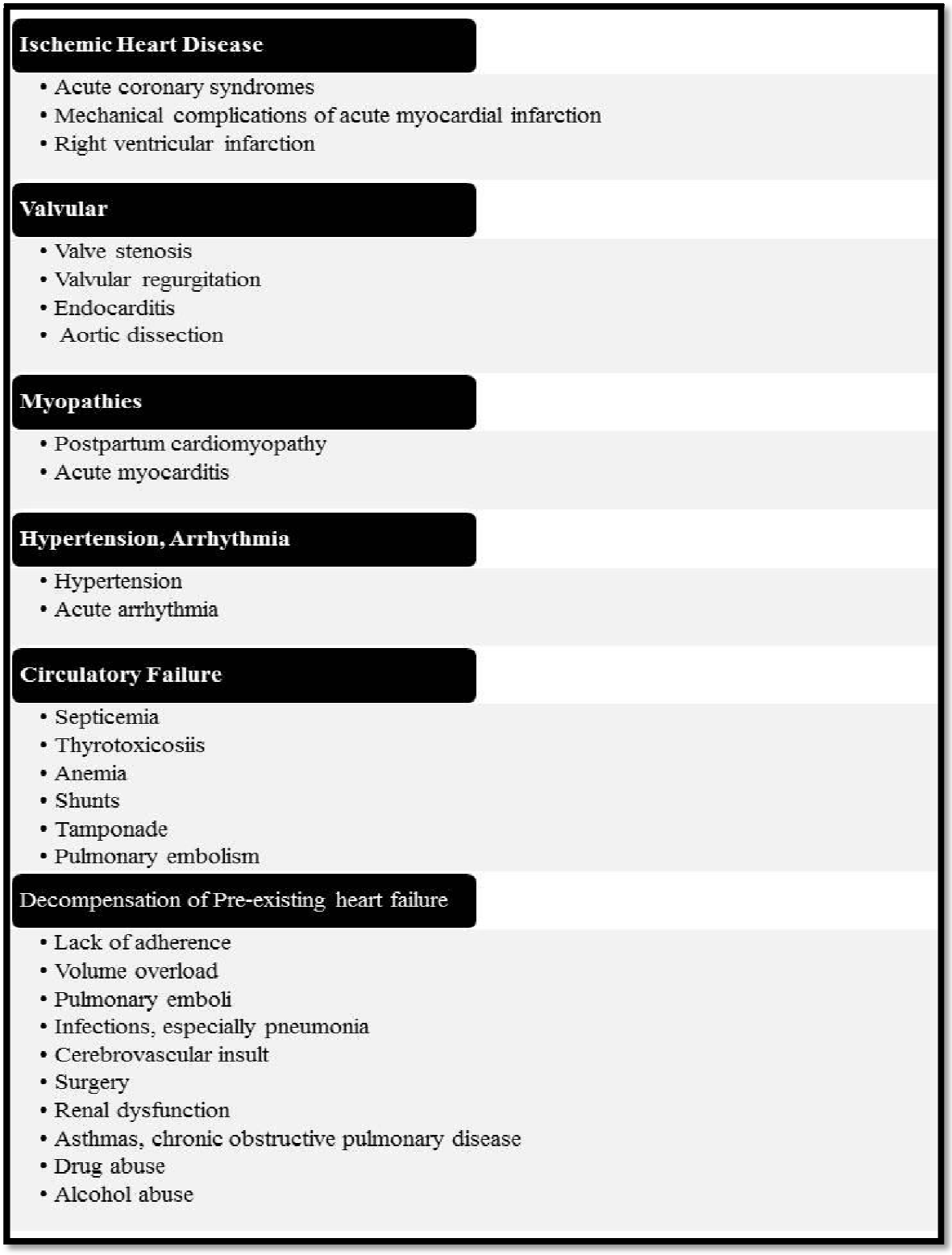


Fig. 6. Causes and precipitating factors of Heart Failure

Pathophysiology:

AHFS comprise a wide range of related disorders resulting in patients presenting with symptoms and signs of acute heart failure. The mechanisms leading to acute decompensation is highly varied and overlapping between patients. These mechanisms are involved in different patients with varying degrees of association. So, a single and simple conceptual model for explaining these pathogenetic mechanisms is not possible. The final common pathway of all these mechanisms leading to symptoms is the onset of pulmonary congestion due to increased left ventricular end diastolic pressure. The pathogenesis can be explained as a consequence of interplay between a pre-existing substrate and mechanisms that initiate and amplify the cardiac dysfunction. (Fig. 7)

The cardiac structure and function is the underlying normal substrate. The cardiac structure and function may be normal or abnormal. Patients with worsening chronic heart failure have an underlying compensated heart failure, which on interaction with initiating and amplifying factors lead to acute decompensation by altering the substrate function. The initiating factors may be extra cardiac or cardiac in origin. In patients with a normal substrate, the initiating mechanism must be strong enough to produce symptoms of decompensation, whereas in patients with abnormal substrate, minor precipitating factors are enough

to cause decompensation. Irrespective of the substrate and initiating factors, various factors amplify the already initiated heart failure. These include inflammatory factors, oxidative stress, injury to the myocardium, neurohumoral factors and other non-cardiac factors like renal failure.[17]

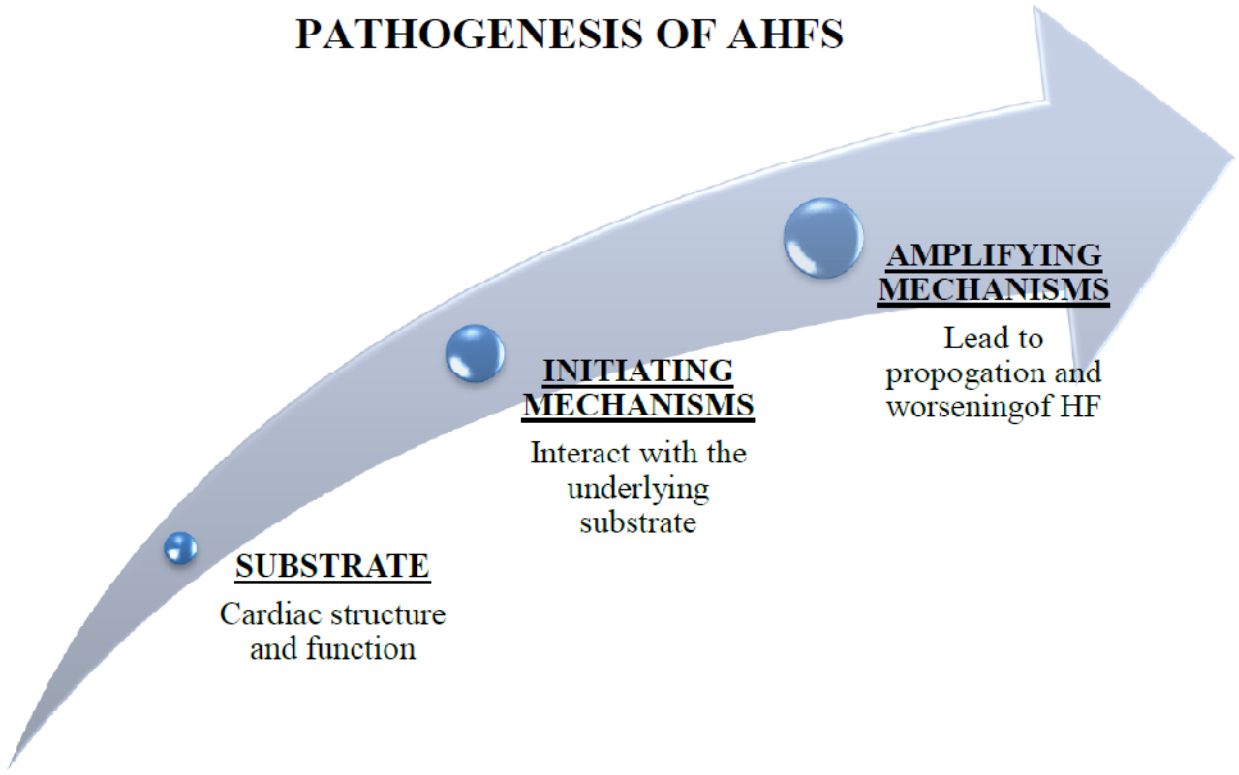


Fig. 7. Pathogenesis of Heart failure syndromes

The final end result in the pathogenesis of AHFS is the onset of pulmonary or systemic congestion, which is the hallmark of heart failure producing most of the symptoms.[18] This congestion is mainly due to the raised left ventricular diastolic pressure in heart failure with reduced ejection fraction. Body weight has

been found to be an important factor, which usually precedes the onset of CHF.[19,20] Congestion, in the initial phases may be asymptomatic, manifesting as hemodynamic congestion – elevated left ventricular filling pressures, which can be diagnosed and monitored by implantable hemodynamic devices. This hemodynamic congestion usually is followed by a phase of clinical congestion, which is manifested by fine end inspiratory basal crackles in the lung fields, elevated JVP and peripheral dependent edema.

Both cardiac and extracardiac mechanisms play an important role in the development of CHF. The impairment in cardiac functions is pivotal in understanding the pathogenesis. The dysfunction may be systolic or diastolic. Impaired pumping of blood from the heart, called systolic failure can trigger variety of adverse mechanisms known as ventricular remodeling, initially thought to be a compensatory phenomenon, at later stages of decompensation can amplify the heart failure.

The most significant mechanisms include the renin angiotensin aldosterone activating system (RAAS) and sympathetic nervous system. Decreased cardiac output leads to hypoperfusion of the kidneys and decreased distal delivery of sodium to distal convoluted tubules. By tubulo glomerular feed back, these mechanisms lead to vasoconstriction, retention of sodium and water, redistribution of fluid from the periphery and hence increase in left ventricular filling pressures

leading to the clinical manifestations. Subsequent activation of neurohumoral mechanisms lead to remodeling of the ventricles and myocyte loss, which further decreases the systolic function ending up in a vicious cycle.(Fig. 8)

Sympathetic oveactivity leading to vasoconstriction and increased peripheral resistance leads to further augmentation of symptoms. Dysfunction of cardiac contractility is essential for the development of acute heart failure, however in about 50% of patients with AHFS have a substantially preserved ejection fraction.[21,22] In these patients, there will be inefficient filling of the ventricles. Isolated diastolic insufficiency rarely leads to AHFS, but it can be a potential substrate for the initiating and amplifying mechanisms causing symptoms of acute decompensation.[23]

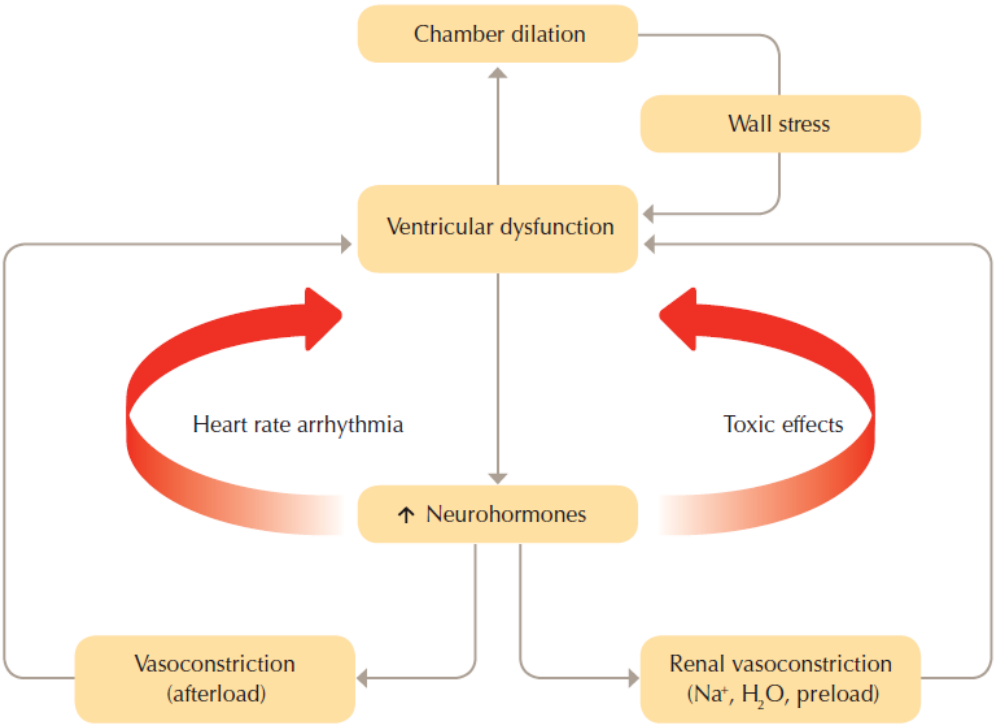


Fig. 8. Role of Neurohormones in the pathogenesis of CHF

Clinical features:

The commonest presenting symptom of CHF is breathlessness, which may be at rest or on exertion depending upon the severity of the heart failure. Exertional dyspnoea, which is seen in 89% of patients with CHF, is due to the congestion in the pulmonary circulation and elevated left ventricular end diastolic pressure.[24] Orthopnoea and paroxysmal nocturnal dyspnoea are more specific for left sided systolic failure.

In patients admitted with CHF, initial assessment gives reliable prognostic information about the patient. An important step in the assessment is the measurement of blood pressure, which defines the clinical spectrum that helps in defining the treatment protocol. Systolic blood pressure, diastolic blood pressure, pulse pressure and orthostatic blood pressure variability may give important information on the pathogenesis of CHF. Systolic pressure is determined by the cardiac output and diastolic pressure by the peripheral resistance, both of which are important determinants of cardiac contractility and ejection fraction. Most patients with CHF have a high or normal systolic blood pressure. A limited number of patients present with clinical hypotension, defined as systolic blood pressure less than 90mm Hg. In patients who have high systolic blood pressure on admission, the increase in blood pressure may be due to compensatory increased sympathetic system activation, which increases the tone of the blood vessels, leading to reactive

hypertension. The systolic blood pressure in this group of patients may return back to normal after treatment is started, whereas some patients may be resistant to the initial treatment. Such patients may require treatment with arterial vasodilators.[25]

The increase in sympathetic tone may also lead to rise in diastolic blood pressure. However, a fall in the diastolic blood pressure indicates peripheral vasodilatation, which may be caused by high output states. An increase in pulse pressure may also be seen in high output states like aortic regurgitation, thyrotoxicosis and anaemia. A decrease in pulse pressure indicates a combination of low cardiac output and systemic vasoconstriction, which is a poor prognostic indicator with 2.5 times increase in mortality risk than with wide pulse pressure.

The general physical examination and assessment of the vital signs will indicate the volume status, the presence and severity of respiratory distress, oxygenation and signs of any other underlying systemic disorder. In all patients with acute decompensation of chronic heart failure, the underlying precipitating factor must be found out for effective treatment outcomes. The presence of altered higher mental functions indicates hypoperfusion of brain. The patient is usually in a propped up position, dyspnoeic, tachypnoeic and diaphoretic and in air hunger due to lactic acidosis.

After the assessment of vital signs, the examination should be concentrated on the neck veins. Jugular venous pressure helps to assess the pressure within the right atrium. Most of the patients presenting with CHF have an elevated jugular venous pressure, which indicates the raised left ventricular filling pressure. The anterior chest wall should be carefully examined for the presence of dyskinetic area in the precardium, which may be indicative of the presence of left ventricular aneurysm.

The position and character of the apical impulse should be determined, which may reveal the underlying cardiomegaly. Careful auscultation may reveal an early diastolic sound (S3), which suggests systolic dysfunction or a late diastolic sound (S4) may be heard in patients with preserved ejection fraction. A systolic murmur may be heard in the apex, suggesting a dilated left ventricle or mitral regurgitation. However, the severity of mitral insufficiency may not correlate with the intensity of the murmur. Examination should also focus on the lung fields to assess the degree of pulmonary congestion, manifesting as fine end inspiratory basal crackles. Percussion of the chest wall should be done and dullness in the base should be looked for to rule out pleural effusion.

Examination of the abdomen may reveal features suggestive of volume overload. The presence of ascites and tender hepatomegaly due to congestive liver caused by long standing right sided heart failure. Most of the

patients present with peripheral oedema, however it should be taken as a sign of heart failure only in the presence of an elevated jugular venous pressure. The severity of congestion can be assessed by clinical, biochemical and dynamic manoeuvres. (Fig. 9)

VARIABLE	Score –1	0	1	2	3
Bedside Assessment					
Orthopnea*		None	Mild	Moderate	Severe or worst
JVP (cm)	<8 and no hepatojugular reflux		8-10 or hepatojugular reflux	11-15	>16
Hepatomegaly	Absent in the setting of normal JVP	Absent	Liver edge	Moderate pulsatile enlargement	Massive tender enlargement extending to midline
Edema		None	1+	2+	3+/4+
Laboratory					
Natriuretic peptides (one)					
BNP		<100	100-299	300-500	>500
NT-proBNP		<400	400-1500	1500- 3000	>3000
Dynamic Maneuvers					
Orthostatic testing	Significant decrease in SBP or increase in heart rate	No change in SBP or heart rate			
6-minute walk test		No difficulty	Mild	Moderate	Severe or worst
6-minute walk test	>400 m	300-400 m	200-300 m	100-200 m	<100 m
Valsalva maneuver	Normal response		Absent overshoot pattern	Square wave pattern	

Fig. 9. Assessment of pulmonary and systemic congestion.Congestion grade: <1, none; 1-7, mild; 8-14, moderate; 15-20, severe. Edema: in the absence of other cause of edema. Orthopnea: 0, absent; 1, mild (use of one pillow); 2, moderate (use of more than one pillow); 3, severe: sleeps in an armchair on in a sitting position.

Prognostic Indicators:

Blood pressure:

Results from the OPTIMIZE-HF study showed that there was a significant association between systolic blood pressure and mortality, across a wide variety of blood pressures. The mortality rate did not increase in patients with high blood pressure and the risk for mortality was lesser than that seen in patients with normal blood pressure.[26] Patients with narrow pulse pressure are at higher risk for mortality and adverse outcomes than with wide pulse pressure.

Renal function:

One of the most important prognostic indicators in patients with heart failure is renal function, assessed by glomerular filtration rate, urea and creatinine. Worsening renal function due to hypoperfusion of kidneys, in the presence of heart failure comes under a group of related disorders called cardio renal syndromes. The risk for both repeated hospitalizations and mortality increases with deteriorating renal function.[27]

Biomarkers:

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are the established and strong predictors for risk of mortality in heart

failure. In patients presenting with CHF, natriuretic peptide levels are powerful prognostic indicators of both long-term and short-term outcomes. BNP levels during admission predicted the in-hospital mortality and mortality at one year in patients with both reduced and preserved systolic function.

Hyponatremia:

About one-fourth of patients presenting with CHF have mild hyponatremia, defined as serum sodium concentration of less than 135 mmol/litre, irrespective of their ejection fractions.[28] Hyponatremia may be dilutional or hypervolemic. The risk for mortality and re-hospitalizations was found to be higher in patients with hyponatremia[29] than normal levels.

Body weight:

Increased body weight is a significant contributor to repeated hospitalizations in ambulatory patients, but not for mortality.[30] Outcome of patients can be improved with appropriate mechanisms to remove the excess fluid.

QRS duration:

Approximately 30 to 40 percentages of patients with acute heart failure and systolic dysfunction have an increased QRS duration of more than 120 milliseconds. It is an indicator of left ventricular dysynchrony and is an

independent predictor of mortality, in spite of appropriate treatment[31] due to arrhythmias.

Coronary Artery Disease:

Patients presenting with CHF due to CAD (Coronary Artery Disease) known as Ischemic dilated cardiomyopathies, have a poor prognosis than patients with heart failure due to other causes. Prognosis depends upon the extent and severity of vascular occlusion, presence of ischaemic or stunned myocardium, collateral formation, duration of ischemia and initial management of the patient.[32,33]

Diagnostic Evaluation:

The pathophysiology of heart failure syndromes being complex, along with the frequent association of co morbidities, a number of specific investigations are required to make an accurate diagnosis. These include biochemical, radiological and interventional investigations.

Biochemical and Haematological anlalysis:

Biochemical and haematological parameters are routinely measured in the initial assessment of patients with heart failure syndromes. These parameters provide essential information on the presence of co morbidities like anemia and

infections that would precipitate and affect the evaluation and management of patients with CHF. Essential parameters like renal functions tests and electrolytes may have to be repeated throughout the course of hospital stay to look for cardio renal syndrome which is important in deciding the treatment modalities. The most common electrolyte disturbance is hyponatremia. About 20% of patients with heart failure have biochemical evidence of hyponatremia.[34] However it has been found that correcting the sodium levels have not improved the clinical course of the patients[35] but predicts mortality. In patients who have been treated for heart failure with diuretics, hypokalemia is common, which is associated with increased risk for cardiac arrhythmias. Hypomagnesemia and hypophosphatemia has also been documented.

Evaluation of renal function should be done for any patient admitted with heart failure and should be monitored periodically. Monitoring is important because renal hypoperfusion can occur with decreased cardiac output, which can decrease the glomerular filtration, leading to acute renal failure. Presence of risk factors like diabetes, hypertension and atherosclerosis further increase the possibility of developing renal failure. Apart from the cardiac failure per se, drugs like angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and diuretics can cause elevation in the renal parameters. Dronedarone, used in the treatment of atrial fibrillation, can cause a rise in serum creatinine values and acute

kidney injury.[36] In patients with CHF, various studies have concluded that about 60% to 70% have reduced glomerular filtration rate[37] and 20% to 30% have raised serum creatinine.[38] Deterioration of renal function during hospital stay is a potent indicator of adverse outcomes.

Diabetes mellitus is an important risk factor in heart failure due to both ischaemic and non-ischaemic aetiology. High levels of glucose in plasma indicate the presence of diabetes and also indicate failure of glycaemic control in already diagnosed patients. Derangements in liver function tests can occur due to haemodynamic alterations or drugs and should be monitored serially. Elevation of serum bilirubin is common in patients with acute decompensation and prolonged congestion leading to cardiac cirrhosis and portal hypertension.

Recent studies have shown that more than one-third of patients with heart failure are anaemic. Lower haemoglobin values have been related with decreased exercise capacity, severe symptoms and increased mortality. Anaemia can be a triggering factor for acute decompensation in a patient with chronic heart failure. Leucocyte count and differential count should be looked into in order to rule out infection as a precipitating factor for decompensation.

Electrocardiogram:

Electrocardiogram (ECG) is an essential component in the initial evaluation of patients with heart failure and also in patients who have been already diagnosed to have heart failure. The commonest finding during decompensation is the presence of sinus tachycardia due to the activation of the sympathetic nervous system. If the patient is already on beta blockers, the sympathetic response may be blunted. Arrhythmias can be a precipitating factor for decompensation, whose correction may dramatically improve the symptoms. In patients with systolic dysfunction, duration of QRS complex exceeding 120 milliseconds indicates ventricular dysynchrony and pro arrhythmic state. QRS duration of more than 120 milliseconds is a major ECG criterion for indication of cardiac resynchronisation therapy. If left ventricular hypertrophy is present, it may indicate the cause of heart failure, including hypertension and valvular heart diseases. The presence of right ventricular hypertrophy indicates pulmonary hypertension, which may be primary or secondary. Previous myocardial infarction is evidenced by the presence of Q waves in the respective leads.

Chest Radiography:

In spite of the advent of newer techniques for the diagnosis of heart failure, chest radiography of the chest still remains to be one of the essential and

gold standard investigations for diagnosing and monitoring treatment in heart failure and ruling out other causes. The classical appearance in chest radiography is the presence of perihilar butterfly pattern of alveolar opacities. The opacities fan out on both sides from the hilar pulmonary arteries to the lung peripheries. Though this is the hallmark finding of pulmonary congestion, most of the patients show only a subtle picture. These include increase in the interstitial marking, manifesting as Kerley B lines, which are horizontal linear opacities ranging up to the surface of the pleura. The other common findings are peribronchial cuffing and increase in the upper lobe vasculature and prominent pulmonary artery markings, which indicate pulmonary hypertension. Cardiomegaly can be made out with posteroanterior projection of the beam. The absence of an enlarged cardiac silhouette shows that the patient has preserved ejection fraction or the onset of systolic dysfunction is recent. Disproportionate or isolated enlargement of the left atrium increases the possibility of mitral valve disease. Enlargement of the right ventricle alone raises the possibility of pulmonary hypertension or right ventricular outflow tract obstruction. Calcification in the valves, coronaries or pericardium may indicate the cause of heart failure. Bilateral pleural effusion can also be made out.

Echocardiography:

The single most useful investigation in the diagnosis and evaluation of patients with heart failure is 2D echocardiography. It is highly essential to establish the underlying cause of heart failure and to plan optimal management strategy for the patient. Two dimensional echocardiography easily diagnose cardiac structural abnormalities or decreased left ventricular systolic function and other cardiac anomalies responsible for heart failure. The left ventricular ejection fraction has been found to be one of the most potent indicators of poor prognosis. In patients with reduced ejection fraction, dilatation of the cardiac chambers is an important finding, as it alters the intracardiac haemodynamics and geometry.[39] Echocardiography also plays an important role in monitoring the response of patients to various modes of treatment.[40-42] It is easily available and widely used diagnostic tool even at the bed side.

One of the most essential prognostic indicators is Left ventricular end diastolic volume which indicates increased left ventricular pressure. Its prognostic value holds good for both ischaemic and non-ischaemic cardiomyopathy. The success of biventricular pacing can be assessed by echocardiography. It can be achieved by assessing the reverse left ventricular remodeling and reduction in

mitral regurgitation. Echocardiography can also predict patients who will be benefited by biventricular pacing.

Magnetic Resonance Imaging:

In the assessment of the anatomy and function of the heart, cardiac magnetic resonance imaging has emerged as an important complement to echocardiography. In the diagnosis of cardiomyopathies and myocarditis, magnetic resonance imaging is the imaging modality of choice, since it has the ability to detect myocardial infiltration, inflammation and scarring. In the setting of renal failure, when gadolinium contrast cannot be used, it can detect the areas of infarction and the viability of the myocardium. However, magnetic resonance imaging should not be performed in patients with pacemakers or implantable cardiac defibrillators.

Treatment Of Heart Failure:

Management of heart failure is dealt with in three phases. Phase I occur in the ICU and deals with immediate stabilization and treatment. Phase II deals with continued management while in hospital and Phase III, the vulnerable phase deals with close monitoring in the early period post discharge, which is gaining more importance[43] since this period is more important in predicting mortality, rehospitalization and adverse outcomes. Biomarkers are particularly

useful in phase III which predicts the early adverse outcomes in the future. The approach to heart failure is depicted in the following figure. (Fig. 10)

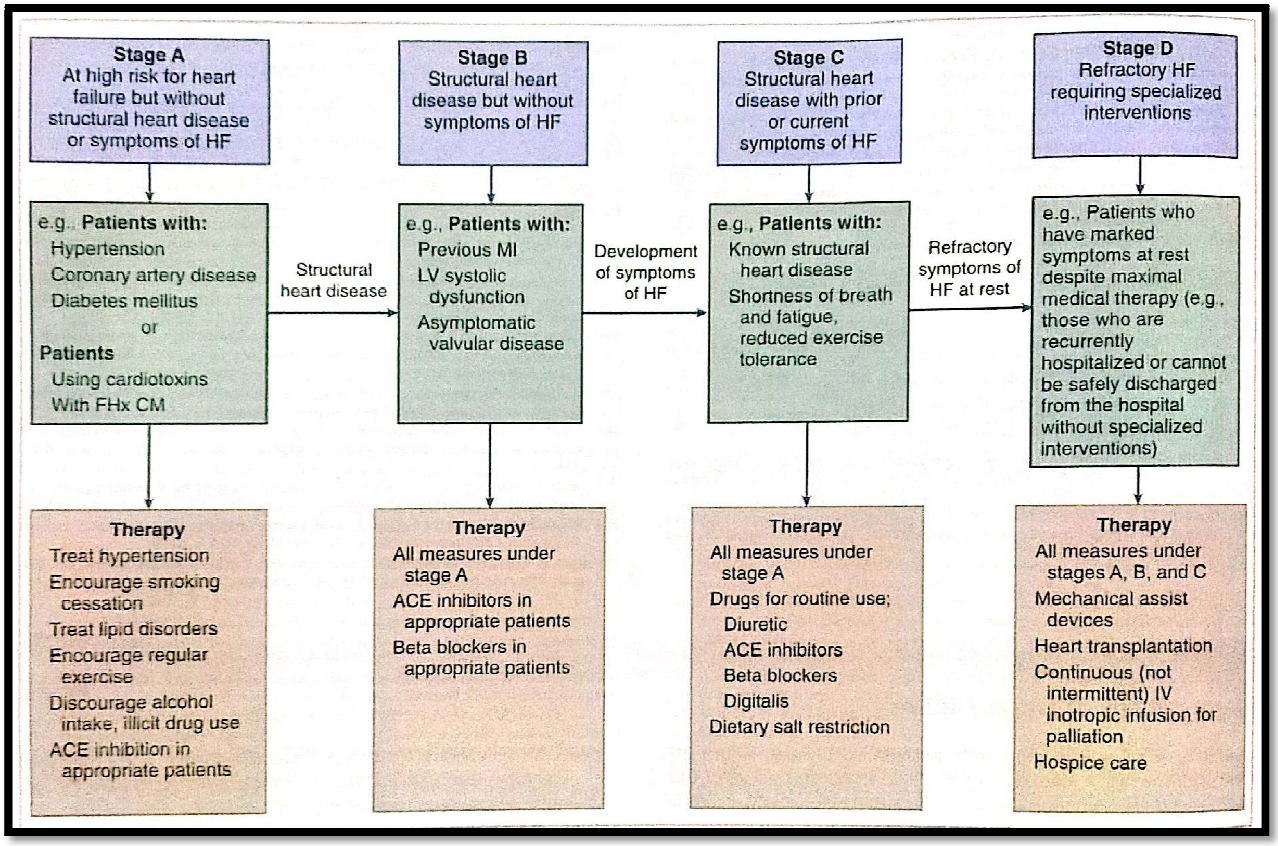


Fig. 10. Approach to a case of Heart failure

In phase I, goal is directed towards prompt recognition and management of life threatening condition like pulmonary oedema, cardiogenic shock and ventricular tachycardia, identification of the initiating mechanism and its prompt treatment and rapid symptom relief.[44] Effort should be made to identify if it is the first episode or worsening of chronic heart failure. In the latter case, a patient is more likely to have a specific cause of HF, such as an acute myocardial

infarction and one or more triggering factors. Based on blood pressure, patients can be divided as hypertensive when systolic BP>160 mm Hg, where presenting feature would be pulmonary oedema, hypotensive when systolic BP<90 mm Hg, when the patient may have right heart failure and normotensive, if patient has acute coronary syndrome. As dyspnea forms the most common symptomatology, the initial management starts with addressing respiratory issues.

After emergency treatment, in Phase II, patient is transferred to ward to relieve symptoms due to pulmonary and systemic congestion and for further workup and planning post discharge. Patients may continue to have breathlessness or volume overload signs like raised JVP, peripheral oedema or, pulmonary crackles, abnormal hemodynamics and neurohormonal mediators due to ventricular remodeling. Many patients get discharged with persistent symptoms with no reduction in body weight.[45] Hence, treatment is to be continued until congestion gets relieved and patient reverts to a state of euvolemia and also function of the myocardium is to be assessed and patients stratified based on whether myocardium would recover function and treated accordingly. Blood pressure, daily weight and fluid balance are to be closely monitored. Serum electrolytes, Serum Uric acid, renal function tests, ABG (Arterial Blood Gas analysis) in case of hypoxia and troponin levels in ACS (Acute Coronary Syndromes) patients should be measured. Intravenous diuretics is converted to oral form and continued to relieve congestion.

Treatment with diuretics is continued till congestive symptoms disappear and orthostatic changes and renal function trend necessitates discontinuation of the drug.

In patients refractory to pharmacologic therapy, excess water and sodium is removed by peripheral ultra filtration. Patients should be advised to undertake simple maneuvers like walking down a corridor or climbing a flight of stairs to assess exercise capacity before discharging the patient. Patient and family should be advised regarding life style modification.

Recurrent admissions are due mainly to early recurring of volume overload features or neurohormonal activation and effects of ventricular remodeling. Patients are to be followed up within one month following discharge. A closer follow up of within a week may be needed based on number of factors which influence readmission or death, the vulnerable phase at which prompt intervention may lead to reduced rehospitalization and reduced risk of death. Early follow up of at risk patients should include measuring blood pressure, renal function, body weight and BNP if possible and to modify therapy when needed. Drug non compliance may also lead to early recurrent pulmonary oedema in early post discharge period.

BIOMARKERS IN HEART FAILURE

Over the past few decades, several cardiac biomarkers have been investigated and a few have been approved for the diagnosis of various cardiac conditions. Some of them also help in determining the future risk, short term and long term mortality. (Fig. 11)

A biomarker should fulfill the following criteria for its significant use in clinical practice.

- The biomarker should be accurate with easy availability at a modest cost so that it can be repeated.
- The biomarker should give information which cannot be retrieved by a thorough clinical examination.
- The measured levels of the biomarker should be useful in making decisions regarding the management of the patient.

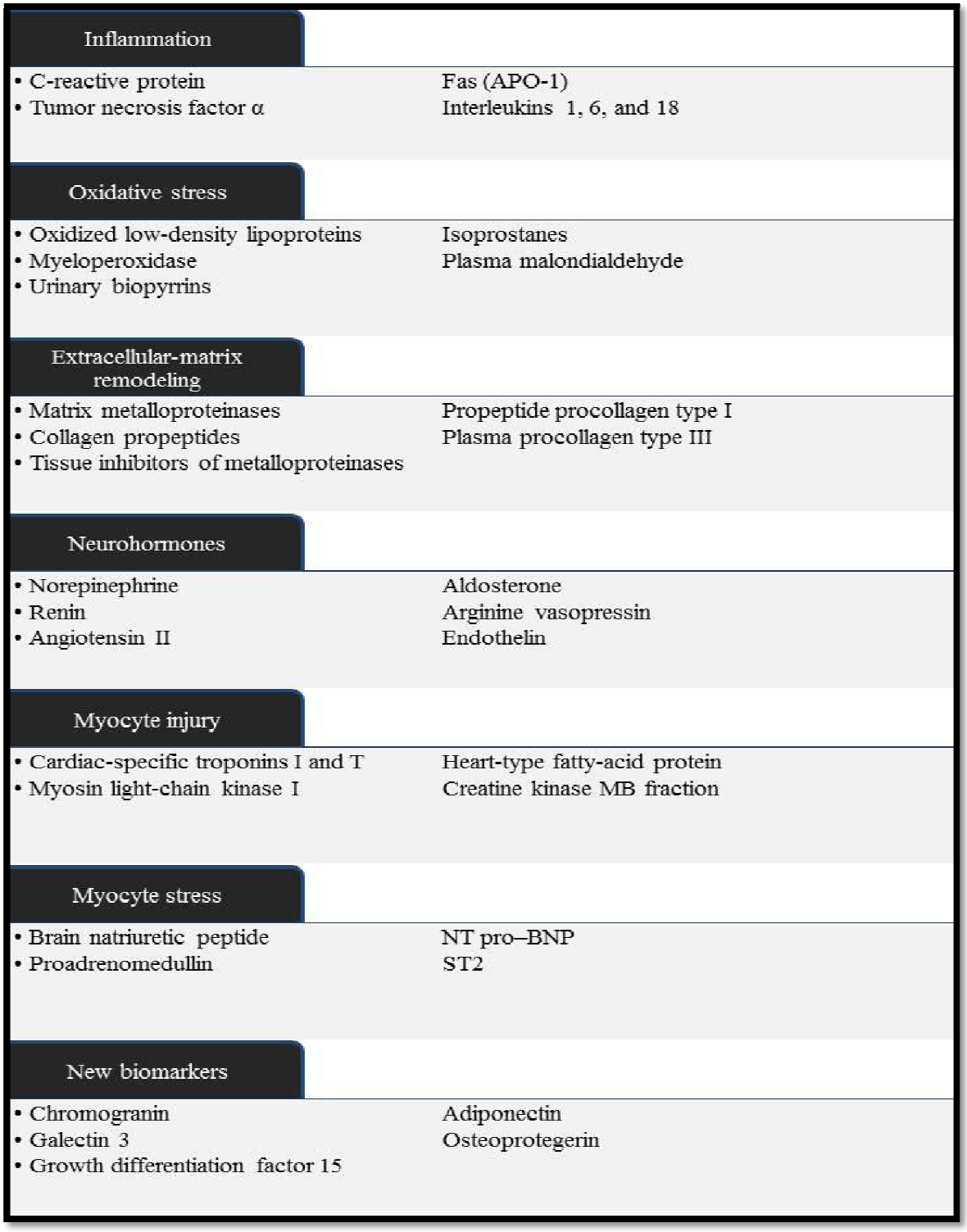


Fig. 11. Biomarkers in Heart Failure

Though, only a few of the cardiac biomarkers satisfy the above mentioned criteria, most of these markers help in providing essential data involved in the pathogenesis of cardiac failure or they may be helpful in the diagnosis of cardiac failure. Some of these markers provide important information regarding the prognosis of the patients and may be useful in risk stratification. Many cardiac biomarkers may be involved in the pathogenesis, which may act as initiating or activating mechanisms, and hence, can be potential targets for specific therapy. The cardiac biomarkers can be classified into the following categories: inflammation, oxidative stress, extracellular matrix remodeling, neurohormones, myocyte injury, myocyte stress and novel markers (Fig 9).[46]

Natriuretic Peptides In Heart Failure

Brain natriuretic peptide is a polypeptide with 32-aminoacids, which is secreted by the ventricles in response to stretching of the ventricular myocardial cells. Calcium ions helps and play a major role in the release of the natriuretic peptides.[47] It was named so since it was first identified in the extracts of porcine brain. However, in humans, it is predominantly produced by the ventricular myocytes. Along with the brain natriuretic peptide, a biologically inactive fragment is also released, known as N-terminal fragment (NT-proBNP). The secreted brain natriuretic peptide binds to the atrial natriuretic factor receptors and

activates them. The physiological actions of this peptide are to decrease the systemic vascular resistance and the central venous pressure by increasing natriuresis. The net effect of natriuretic peptide is a decrease in the net blood volume, leading to reduction in the systemic blood pressure and afterload (peripheral resistance), which causes an increase in contractility and the cardiac output by means of an increased ejection fraction.

It has been demonstrated in various studies that brain natriuretic peptide levels correlated very well with symptoms of heart failure[47-51]and remains an established cardiac biomarker. The level of natriuretic peptides correlates well with the left ventricular systolic function, assessed by the ejection fraction by means of echocardiography.

Certain large studies have shown that NT-proBNP is the most sensitive biomarker for the detection of mild left ventricular systolic dysfunction. However, since these patients were relatively asymptomatic, the clinical significance is unclear.[52] Of all the biomarkers studied in heart failure, brain natriuretic peptide has emerged as the biomarker of choice in the diagnosis and risk stratification of patients with heart failure.

Troponins In Heart Failure:

Over the past decade, troponins have emerged as the gold standard biomarker for the diagnosis of acute coronary syndromes (ACS), especially acute myocardial infarction. However, troponins may be elevated in conditions other than acute coronary syndromes. One such condition is heart failure. It has been proposed that cardiac troponins are strong predictors for poor prognosis and adverse outcomes throughout the spectrum of pathogenesis of heart failure syndromes.[53] Troponin elevation has been on the rising trend in patients with heart failure, even in the absence of significant coronary ischaemia. This situation complicates the interpretation of the elevated troponins in making the diagnosis of acute myocardial infarction. However troponins are still one of the important tools in the diagnosis of acute coronary syndromes. Recently, highly sensitive assays have been used to detect troponins, resulting in the increase of abnormal results in patients with heart failure.[54-58]

Troponins are special proteins essential for the control of both cardiac and skeletal muscle contraction. There are two chief proteins involved in the contraction-relaxation cycle of the muscles, namely actin and myosin. Calcium is essential for the initiation of contraction of muscles. It initiates muscle contraction through the troponin complex.

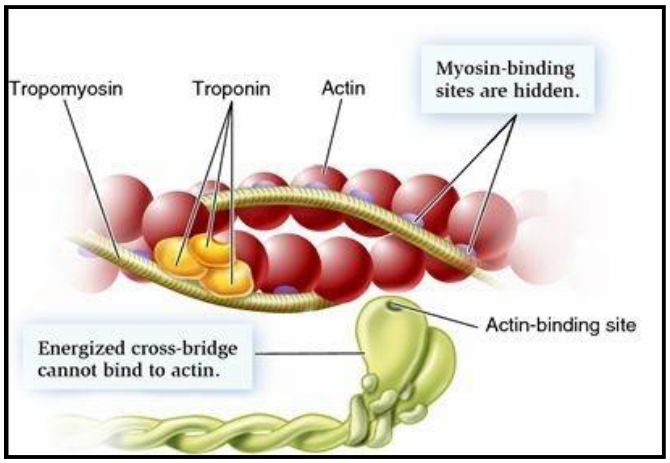


Fig.12. Troponin complex

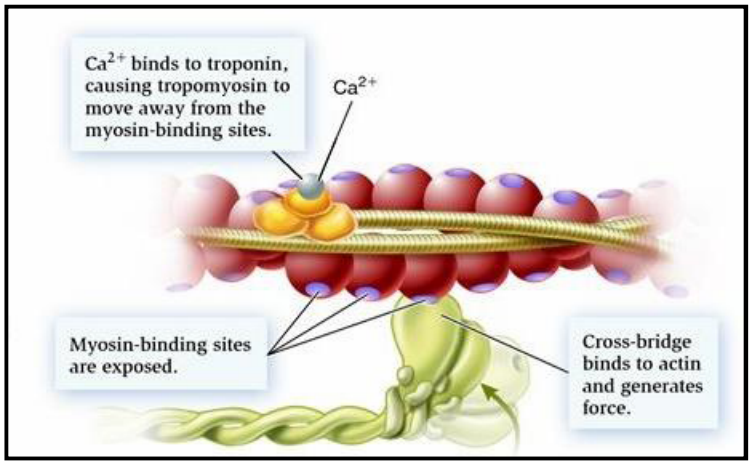


Fig. 13. Role of troponins in muscle contraction

Measurement of Troponins

The troponin complex comprises three proteins namely Troponin C (calcium binding), Troponin T (tropomyosin binding proteins) and Troponin I (inhibitory) (Fig. 12).They are not involved in the contraction of smooth muscles. Separate genes are responsible for skeletal and cardiac isoforms and therefore, the

isoforms vary in structure. Cardiac troponin I is not represented by damaged skeletal muscles and hence, it is highly specific for cardiac muscle injury.[59,60]

In the relaxed state, the binding site for actin with myosin is inhibited by the cardiac troponin I (cTnI). Binding of calcium with the cardiac troponin C (cTnC) initates a complex mechanism by which the cardiac troponin I uncovers the active binding site on the actin molecule, making it available for binding with the myosin chain resulting in contraction of the muscles. (Fig. 13)

Background: Serum Uric Acid (UA)

Although the discussion regarding whether serum uric acid (UA) is a risk factor for the development of either cardiovascular disease or renal disease is currently controversial,[61,62] its role as a prognostic risk marker for these diseases, especially for those with hypertension, diabetes mellitus or cardiac failure, seems to be well accepted. Higher UA levels are accepted as a progressive marker for the risk of developing either coronary heart diseases, or cerebrovascular accidents like stroke when comparing to the populations with normal uric acid concentration, particularly those in the lower one third of the physiological range. [61,63-73]

An article published earlier by LK Niskanen's *et al*. showed that increased uric acid concentrations in serum were independent of the variables commonly associated with gout or metabolic syndrome in relation with cardiovascular disease mortality among middle aged men.[73] Hyperuricemia in CHF is due to overproduction of uric acid in contrary to gout in which hyperuricemia is mainly due to decreaed renal excertion and hence the pathophysiology of hyperuricemia in CHF and gout varies.

There exist a controversy regarding whether serum uric acid is a risk factor or a risk marker, and also whether uric acid is an antioxidant or pro oxidant, but it is vital to understand that UA is associated with endothelial cell dysfunction or damage, reduced bioavailability of endothelial nitric oxide (eNO) and interaction with other toxic substrates and reactive oxygen species (ROS) of the A-FLIGHT-U acronym, which can result in accelerated atherosclerosis (Fig. 14).[74]

Johnson RJ *et al.* shows that elevated serum uric acid concentrations can predict the development of future cardiovascular diseases among the general population, among the hypertensive individuals, and in those individuals with previous history of cardiovascular disease. Moreover it also showed that elevated serum uric acid can predict the occurrence of hypertension[71] in general population.

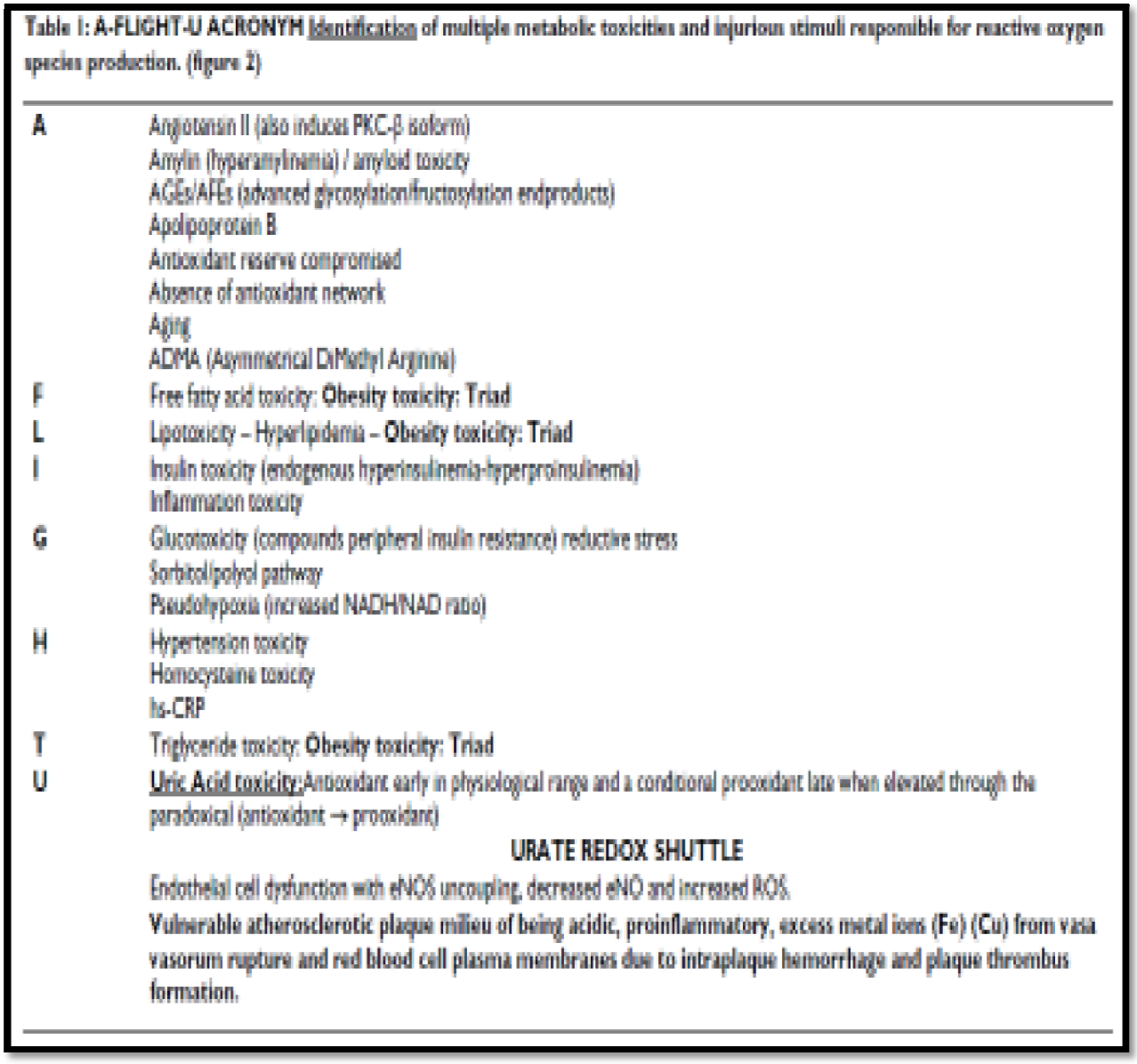


Table I: **A-FLIGHT-U ACRONYM** Identification of multiple metabolic toxicities and injurious stimuli responsible for reactive oxygen species production. (figure 2)

A	Angiotensin II (also induces PKC-β isoform) Amylin (hyperamylinemia) / amyloid toxicity AGEs/AFEs (advanced glycosylation/fructosylation endproducts) Apolipoprotein B Antioxidant reserve compromised Absence of antioxidant network Aging ADMA (Asymmetrical DiMethyl Arginine)
F	Free fatty acid toxicity: **Obesity toxicity: Triad**
L	Lipotoxicity – Hyperlipidemia – **Obesity toxicity: Triad**
I	Insulin toxicity (endogenous hyperinsulinemia-hyperproinsulinemia) Inflammation toxicity
G	Glucotoxicity (compounds peripheral insulin resistance) reductive stress Sorbitol/polyol pathway Pseudohypoxia (increased NADH/NAD ratio)
H	Hypertension toxicity Homocysteine toxicity hs-CRP
T	Triglyceride toxicity: **Obesity toxicity: Triad**
U	Uric Acid toxicity: Antioxidant early in physiological range and a conditional prooxidant late when elevated through the paradoxical (antioxidant → prooxidant) **URATE REDOX SHUTTLE** Endothelial cell dysfunction with eNOS uncoupling, decreased eNO and increased ROS. **Vulnerable atherosclerotic plaque milieu of being acidic, proinflammatory, excess metal ions (Fe) (Cu) from vasa vasorum rupture and red blood cell plasma membranes due to intraplaque hemorrhage and plaque thrombus formation.**

Fig. 14. A-Flight-U Acronym

Some groups of patients are more prone to develop early cardiovascular disease due to premature atherosclerosis compared to the general population. They include Diabetes with accelerated atherosclerosis, non-diabetic patients with accelerated atherosclerosis, decompensated cardiac failure patients with ischemic cardiomyopathy, metabolic syndrome patients (those with

constellation of obesity, insulin resistance, impaired glucose tolerance, hypertension and dyslipidemia), chronic kidney disease patients, hypertensive patients, African American patients, those patients consuming long term diuretics, and those patients with excess alcohol consumption. Each of this patient groups have a specific mechanism which leads to their respective disease leading to hyperuricemia (Fig. 15)[74]

Table 2: Hyperuricemia: clinical clusters at cardiovascular risk

GROUPS	Abbreviated Mechanisms
Patients with CVD Accelerated atherosclerosis Congestive heart failure	Increased apoptosis – necrosis of the arterial vessel wall and capillary resulting in increased purine metabolism and hyperuricemia. Increased oxidative – redox stress Antioxidant – Prooxidant Paradox: Urate Redox Shuttle
Patients with (T2DM) Accelerated atherosclerosis (Atherosclerosis)	Acting through obesity and insulin resistance. Accelerated atherosclerosis with increased vascular cell apoptosis and inflammatory necrosis with increased purine metabolism resulting in hyperuricemia and increased oxidative stress through ischemia-reperfusion and xanthine oxidase. Additional reductive stress associated with glucotoxicity and pseudohypoxia. Increased oxidative-redox stress Antioxidant – Prooxidant Paradox: Urate Redox Shuttle
Obesity – Insulin resistance Hyperinsulinemia – Insulin toxicity Metabolic Syndrome (figure 1): Hyperinsulinemia Hypertension Hyperlipidemia dyslipidemia, obesity Hyperglycemia	Leptin may induce hyperuricemia. Insulin increases sodium reabsorption and is tightly linked to urate reabsorption. Increased oxidative – redox stress Antioxidant – Prooxidant Paradox: Urate Redox Shuttle
Men and Postmenopausal females Renal diseases Hypertension	Estrogen is uricosuric Decreases in GFR increases uric acid levels Urate reabsorption increased in setting of increased renal vascular resistance, microvascular disease predisposes to tissue ischemia that leads to increased urate generation (excess purine metabolism) and reduced excretion (due to lactate competing with urate transporter in the proximal tubule). Increased oxidative – redox stress Antioxidant – Prooxidant Paradox: Urate Redox Shuttle
African American Diuretic use Alcohol use (in excess)	Unknown (assumed genetic causes as yet unidentified) Volume contraction promotes urate reabsorption Increases urate generation and decreased urate excretion

Fig. 15. Hyperuricemia: clinical clusters at cardiovascular risk

Along with the common finding of increased oxidative-redox stress among these patient groups, they also exhibit insulin resistance and metabolic syndrome.

URIC ACID METABOLISM

The final oxidation product after catabolism of purines in humans is uric acid. Urates are the ionized forms of uric acid and greater than 95% occur as mono sodium urate crystals at pH 7.4 in plasma extracellular fluid and synovial fluid.[75]

The pH of urine influences the solubility of uric acid in solutes to a major extent. Purines can be synthesized and catabolized in almost all tissues of the body, but urates can be produced only in those tissues with xanthine oxidase activity such as liver and small intestine. The amount of urate produced varies according to the amount of purines present in the diet and also according to the amount synthesized, metabolised or degraded. Normally around 75% of the urate produced is excreted by the kidneys and major portion of the remainder by the small intestine.

The kidneys utilize specific transporters like organic anion transporters (OATs) like urate transporter 1 (URATI) and human uric acid transporter (hUAT) to clear urate from the plasma and maintain physiologic balance. URAT1 and other OATs carry urate into the tubular cells through the apical side of the lumen, then after entering into the cell, passes to the basolateral side of the lumen by a process controlled by the voltage dependent carrier hUAT.

There are four steps in the handling of uric acid by the kidneys. The processes are

(1) Glomerular filtration,

(2) Tubular reabsorption

(3) Secretion, and

(4) Post-secretory reabsorption.

The anion transporter URAT1 is usually present at the apical brush border of the proximal nephron and are directly inhibited by uric acid compounds on the apical side of the tubular cell by the so-called cis-inhibition.[76] The amount of total body urate is the net balance between urate production and urate excretion. The amount of urate produced varies directly according to the amount of purines ingested in the diet and also according to the amount synthesized, salvaged or degraded. Normally maximum amount of the urate produced is excreted by the kidneys and major portion of the remainder by the small intestine. Hyperuricemia can be caused by either increasing the production, decreasing the excretion, or by the combination of those mechanisms. When hyperuricemia exists, urate can precipitate in vivo and deposit in tissues as tophi. (Fig. 16)

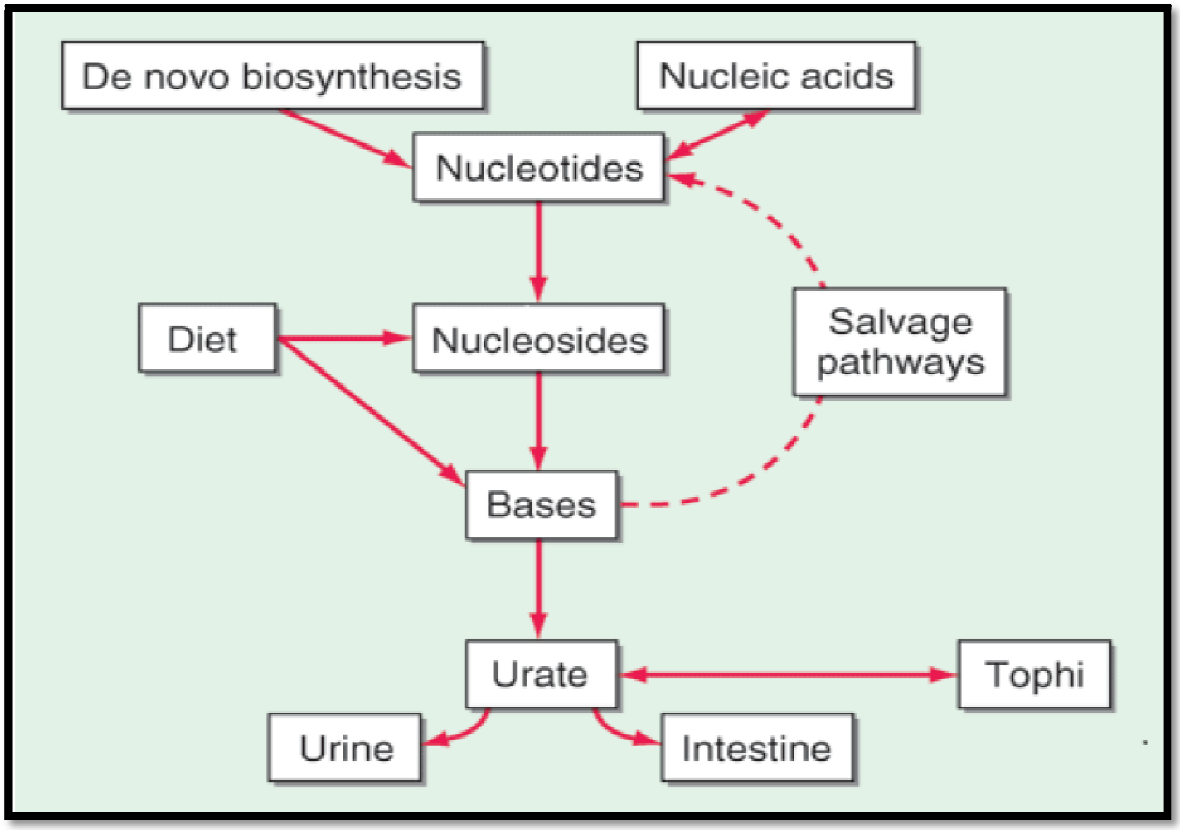


Fig. 16. Uric acid turnover and metabolism

HYPERURICEMIA

Based on the epidemiologically, physiochemical and disease burden criteria, hyperuricemia is defined as an elevation of plasma (or serum) urate level greater than 420 umol/L (7.0 mg/dL). Epidemiologically considering, hyperuricemia can be defined as a mean plus two standard elevations of serum uric acid values from a randomly selected population. When estimated among the unselected population, 95% of them have a serum uric acid less than 420 umol/L (7.0 mg/dL). Considering physicochemically, hyperuricemia is the amount of urate

in the plasma which exceed the solubility limits of monosodium urate >415 umol/L (6.8 mg/dL).

Lastly, we can define hyperuricemia according to the risk of developing disease. The chance of an individual developing urolithiasis or gouty arthritis increases 3 fold when the urate concentration in the blood exceeds 420 umol/L (7.0 mg/dL) and increases in direct proportion to further increase in the concentrations > 7.0 mg/dl. Hyperuricemia is present in around 2.0 to 13.2% of ambulatory adults and to an increased frequency in hospitalized individuals. [77]

Causes of Hyperuricemia

Hyperuricemia can be caused by either a primary (when the cause is due to an innate mechanism) or a secondary (due to any acquired disorder) mechanism. But it is more useful to classify hyperuricemia based on the circumstances that lead to the elevation in serum uric acid such as either increased urate production, or reduced urate excretion or a combination of the above two mechanisms.

Pathophysiological Classification of Hyperuricemia:

1) Urate overproduction

    a) Primary idiopathic

    b) HPRT deficiency

    c) PRPP synthetase overactivity

d) Hemolytic process

e) Lymphoproliferative diseases

f) Myeloproliferative diseases

g) Psoriasis

h) Paget’s disease

i) Glycogenosis III, V, and VII

j) Rhabdomyolysis

k) Exercise

l) Alcohol

m) Obesity

n) Purine-rich diet

2) Decreased Uric acid Excretion

a) Primary idiopathic

b) Renal insufficiency

c) Polycystic kidney disease

d) Hypertension

e) Acidosis

i) Lactic acidosis

ii) Diabetic ketoacidosis

f) Starvation ketosis

g) Berylliosis

h) Sarcoidosis

i) Lead intoxication

j) Hyperparathyroidism

k) Hypothyroidism

l) Toxaemia of pregnancy

m) Bartter's syndrome

n) Down syndrome

o) Drug ingestion

i) Salicylates (>2g/d)

ii) Diuretics

iii) Alcohol

iv) Levodopa

v) Ethambutol

vi) Pyrazinamide

vii) Nicotinic acid

viii) Cyclosporine

3) Combined Mechanism

a) Glucose-6- phosphatase deficiency

b) Fructose-1- phosphate aldolase deficiency

c) Alcohol

d) Shock

Increased Urate Production

The purine content in the diet is an exogenous source of purines and contributes to the major source of urate in the body. Dietary restriction of purines itself approximately decreases serum urate level by 60umol/L (1.0 mg/dL) and decreases the excretion of uric acid in the urine by atleast 200 mg/day. The food items with high nucleic acid content contributes significantly to more serum urate concentration, because about 50% of ingested RNA purine and 25% of ingested DNA purine is metabolized into the urine as uric acid. Examples of such foods rich in purines include liver, "sweetbreads" (i.e., thymus and pancreas), kidney, and anchovy.

The serum urate level is also enhanced by endogenous sources of purine production which contributes less than dietary purines. De novo purine biosynthesis is an eleven-step process that results in formation of *inosine monophosphate (IMP)* and the formation of purine ring from non purine ring structures. The initial step is the combination of *phosphoribosylpyrophosphate (PRPP)* with *glutamine* and is catalyzed by *amidophosphoribosyltransferase (amidoPRT)* which is the rate limiting step and plays a major role in purine biosynthesis and urate production. (Fig. 17)

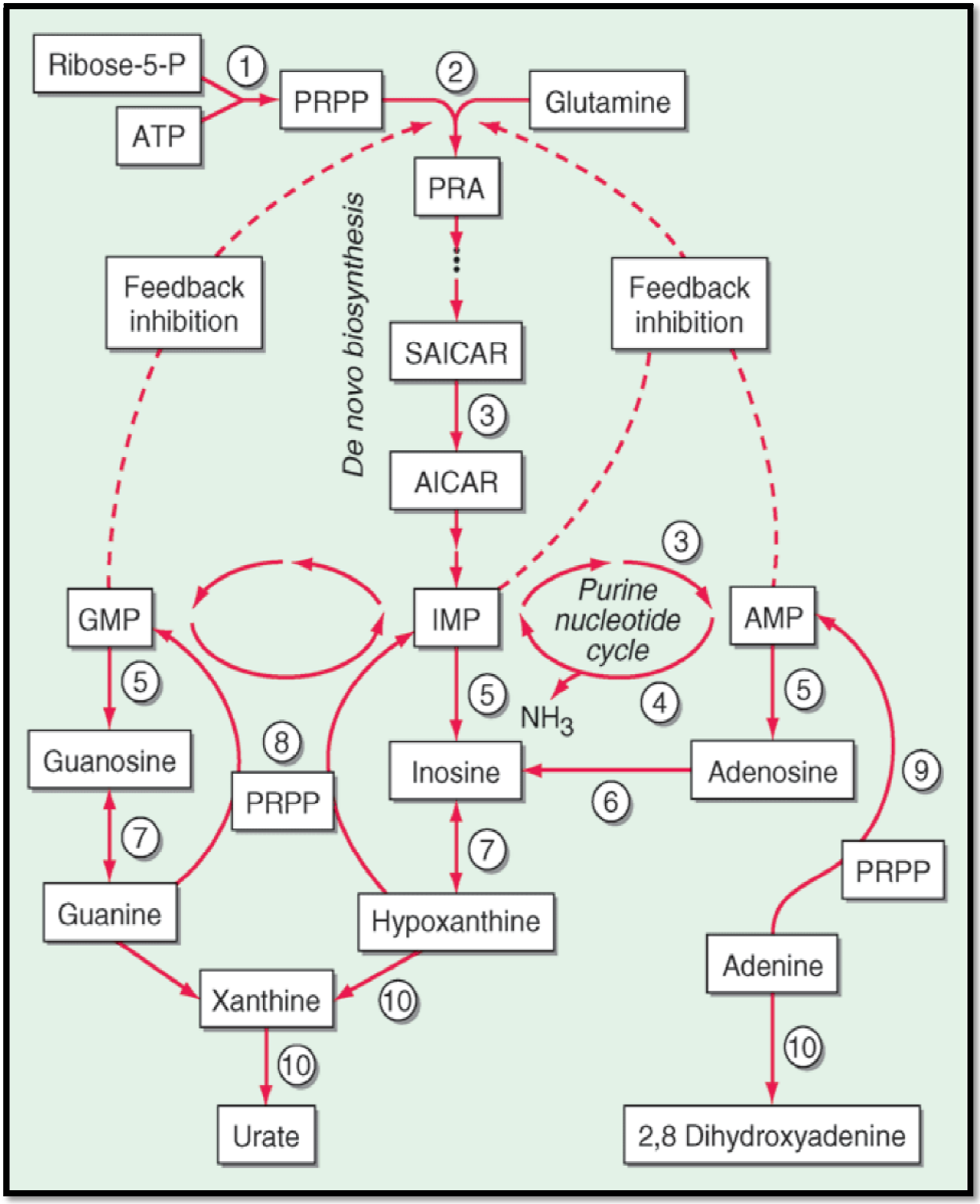


Fig. 17. De novo biosynthesis and metabolism of Purine nucleotides

1- Phosphoribosylpyrophosphate(PRPP) synthetase

2- Amidophosphoribosyltransferase (amidoPRT)

3- Adenylosuccinate lyase

4- (myo-)adenylate (AMP) deaminase

5- 5'-nucleotidase

6- Adenosine deaminase

7- Purine nucleoside phosphorylase

8- Hypoxanthine phosphoribosyltransferase (HPRT)

9- Adenine phosphoribosyltransferase (APRT)

10- Xanthine oxidase

Another regulatory pathway in purine synthesis involves the salvage of purine bases by enzyme *hypoxanthine phosphoribosyltransferase (HPRT).* HPRT catalyzes the reaction of the purine bases hypoxanthine and guanine with PRPP to form the ribonucleotides Inosine monophosphate (IMP) and guanosine monophosphate (GMP) respectively. Increased salvage activity of HPRT increases the IMP and GMP concentrations and decreases the de novo synthesis of purines and uric acid, thus retards de novo synthesis by increasing the concentrations of inhibitory ribonucleotides.[77]

Serum urate levels are proportional to the rates of de novo purine biosynthesis, which is determined by the level of PRPP, as evidenced by the

occurrence of two inborn errors of purine metabolism. Increased PRPP synthetase activity and HPRT deficiency are associated with increased production of purines, hyperuricemia, and hyperuricaciduria. An inborn error of purine synthesis can lead to increase uric acid production. An X-linked disorder that causes an increase in the activity of the enzyme PRPP synthetase can lead to increased PRPP production and accelerated de novo biosynthesis. PRPP is the substrate and allosteric activator of amidoPRT, which is the first and rate limiting enzyme in the de novo pathway.

Another inborn error of de novo purine synthesis leading to hyperuricemia is HPRT deficiency, which is also an X-linked disorder which enhances urate biosynthesis in two ways. Firstly PRPP is accumulated as a result of a decrease in utilization in the salvage pathway which in turn, provides increased substrate for amidoPRT and de novo biosynthesis. Secondly in addition, reduced formation of the nucleoside monophosphates, IMP and GMP, through the salvage pathway impairs feedback inhibition on amidoPRT, further enhancing de novo biosynthesis leading to hyperuricemia.

Accelerated purine nucleotide degradation may also cause acute hyperuricemia, as a part of tumour lysis syndrome which is a medical emergency i.e., with conditions of rapid cell turnover, proliferation, or cell death, as in leukemic blast crisis, cytotoxic therapy in malignancy, hemolysis, or

rhabdomyolysis. The nucleic acids released from cells are metabolized rapidly by nucleases and phosphodiesterases, forming increased uric acid levels.

Hyperuricemia can also occur via catabolic pathways by the breakdown of ATP of skeletal muscle after strenuous exercise or seizure activity. It is also seen in glycogen storage diseases type III, V and VII. Serum uric acid is also increased in acute stressful situations like myocardial infarction, cerebrovascular accident, acute respiratory failure and in smoke inhalation, all of which leads to increased catabolism of ATP.[77]

Decreased Uric Acid Excretion

Majority of individuals with hyperuricemia have a defect in the renal excretion of uric acid. In gout, the hyperuricemia is mainly due to decreased urate clearance to glomerular filtration rate (or urate to insulin clearance rate). Thus, gouty individuals excrete about 40% less uric acid than nongouty individuals for any given plasma urate concentration. Uric acid excretion increases in both gouty and nongouty individuals when plasma urate levels are increased beyond 7 mg/dl, but in those with gout, plasma urate concentrations should be 1 to 2 mg/dL higher than normal to achieve near equivalent uric acid excretion rates.[77]

Abnormal uric acid excretion can result due to either of three mechanisms: reduced glomerular filtration, increased reabsorption or decreased tubular secretion. Reduced urate filtration does not cause primary hyperuricemia

but it contributes to the elevation in uric acid in renal dysfunction. Hyperuricemia is invariably present in chronic kidney disease, but the correlation between uric acid levels and glomerular filtration rate is poor. Uric acid excretion per unit of glomerular filtration rate gradually increases progressively, tubular reabsorptive capacity is reduced, and the extrarenal clearance of uric acid increases but tubular secretory capacity tends to be preserved as kidney damage becomes more severe in chronic kidney disease. The secondary hyperuricemia found in acidosis is due to the decreased tubular secretion of uric acid.

Alcohol intoxication, starvation, diabetic ketoacidosis, salicylate poisoning and lactic acidosis all lead to accumulation of acids such as acetate, acetoacetate, β hydoxybutyrate, salicylates and lactate indirectly leading to hyperuricemia by competing with uric acid for tubular secretion. Hyperuricemia can also be due to increased reabsorption of urate at a site distal to its tubular secretion which is responsible for the hyperuricemia of extracellular volume depletion which occurs with diabetes insipidus or diuretic therapy.[77]

Combined Mechanisms

Both increased urate production and decreased uric acid excretion can together contribute to hyperuricemia. In individuals with a deficiency of glucose-6-phosphatase (an enzyme that hydrolyzes glucose-6- phosphate to glucose), increase in urate production results from accelerated ATP degradation at times of fasting or

hypoglycaemia and in addition, the lower levels of nucleoside monophosphates decrease feedback inhibition by amidoPRT, further increasing de novo biosynthesis. These patients are hyperuricemic from infancy itself and develop early gout. These individuals also develop hyperlacticacidemia, which block uric acid excretion by reducing tubular secretion.

Patients with hereditary fructose intolerance caused by fructose-1-phosphate aldolase deficiency produce hyperuricemia by both mechanisms. In these patients, the heterozygous state occurs in 0.5 to 1.5%, which is relatively a common cause of familial gout.[77] In homozygous states, fructose ingestion causes vomiting and hypoglycemia leading to hepatic failure and proximal renal tubular dysfunction. Ingestion of fructose, the substrate for the enzyme causes accumulation of fructose-1-phosphate because of enzyme deficiency causes ATP depletion, accelerated purine nucleotide catabolism, and leading to hyperuricemia. Both lactic acidosis and renal tubular acidosis contribute to urate retention. Those heterozygous carriers develop hyperuricemia, and only one-third develop gout.

Alcohol can also promote hyperuricemia by both mechanisms. Excess alcohol consumption causes hepatic breakdown of ATP and can increase urate production. Alcohol consumption may also induce hyperlacticacidemia, which can block uric acid secretion indirectly resulting in high uric acid levels. The higher

purine content in some alcoholic beverages such as beer can also cause hyperuricemia.

Uric acid, Metabolic syndrome, Diabetes mellitus, and Atherosclerosis

Kylin et al. in 1923 first highlighted the significance of clustering the group of metabolic disorders namely: hyperglycemia, hypertension and hyperuricemia.[76] After the information from seminal Banting lecture, Reaven GM in 1988, noted the major role of insulin resistance and described Syndrome X, which is now also known as insulin resistance syndrome (IRS) or metabolic syndrome(MS).[78] Reaven GM and Zavaroni I et al in 1993, seventy years after Kylin described the clustering phenomenon, suggested that hyperuricemia is also included along with the metabolic and hemodynamic abnormalities associated with hyperinsuinemia of syndrome X or IRS.[79]

Hyperglycemia, hyperinsulinemia, hypertension and dyslipidemia are the major components of metabolic syndrome. It is well established that each one of these factors individually can be risk factor for cardiovascular mortality and morbidity, but together they forms a deadly quartet that causes premature atherosclerosis in non-diabetics as well as the atherosclerosis related to metabolic syndrome.

It can also be noted that uric acid is linked to chronic inflammation. Hyperuricemia, highly sensitive C reactive protein (hsCRP), reactive oxygen species (ROS) and homocysteine act concordantly to accelerate the atherosclerosis associated with syndrome X. They cause remodeling of the arterial vessel wall endothelial lining causing atherosclerosis progression. The syndrome X has been known by multiple names and has been renamed numerous times, highlighting its significance in determining cardiovascular morbidity and mortality. In order to help the clinicians to workup for increased risk for cardiovascular mortality, these factors had been included in the National Cholesterol Educational Program- Adult Treatment Panel III (NCEP ATP III) guidelines recently.[76,78-80]

Hyperinsulinemia and Hyperamylinemia

The renin angiotensin aldosterone system is activated by insulin, proinsulin and amylin, synergistically, to produce angiotensin II. Angiotensin II is one the most powerful inducers of the enzyme NAD(P)H oxidase resulting in increase of NAD(P)H levels, leading on to an increase in vascular reactive oxygen species and free radicals like superoxide ($O2^{-}$).[80,81] Thus Hyperinsulinemia in addition to retention of water, sodium, potassium, also causes hyperuricemia which causes many deleterious effects of free radical injury. (Fig. 18)[82]

Table 3: Deleterious effects of hyperinsulinemia (HI)

1.	HI, hyperproinsulinemia, and hyperamylinemia synergistically activate RAS with subsequent increase in Ang II, renin, and aldosterone.
2.	HI promotes Na^+ and H_2O retention, which increases blood volume and pressure. In turn this activates the reabsorption of uric acid resulting in elevation of SUA. In turn increased SUA has been shown to increase tubular reabsorption of Na+.
3.	HI increases membrane cation-transport increasing intracellular Ca^{++}, which increases tone and pressure.
4.	HI activates the sympathetic nervous system.
5.	HI stimulates vSMC proliferation and migration and remodeling.
6.	HI increases the number of AT-1 receptors.
7.	HI creates cross talk between the insulin receptor and AT-1 receptor, resulting in a more profound Ang II effect.
8	HI promotes PI3 kinase Akt-MAP kinase Shunt. Impairing the metabolic (PI3 kinase-AKT pathway while promoting the MAPkinase remodeling pathway.
9.	HI induces Ang II, which promotes the MAP kinase pathway and remodeling.
10.	HI induces Ang II, which is the most potent stimulus for production of NAD(P)H oxidase with reactive oxygen species generation (superoxide production) and resultant vascular oxidative stress.

Fig. 18. Deleterious effects of Hyperinsulinemia

Hypertension

Studies have shown that hyperuricemia is strongly associated with hypertension. It has found that about 25% of untreated hypertensives, 50% of those treated with diuretics and 75% of those who presented with malignant hypertension have evidence of hyperuricemia.[83] The proposed explanations for the relation between hyperuricemia and hypertension are:

1. Urate reabsorption is stimulated by decreased GFR in hypertensives.

2. Ischemia of the tissue caused by hypertensive microvascular disease.

3. Increased lactate production due to the ischemia, competes with urate for tubular secretion.

4. Increased breakdown of RNA-DNA leading to increased catabolism of purines causing increased uric acid by the exaggerated action of xanthine oxidase in hypertensive individuals. (malignant hypertension)

5. Xanthine oxidase and ROS is induced by the presence of ischemia which leads to increased uric acid levels. This explains the possible cause for the rise in uric acid levels in congestive cardiac failure and preeclampsia.

Lin KC et al studied that blood pressure levels and serum uric acid levels were synergistically indicative of cardiovascular morbidity.[84] Experiments done in two separate laboratories on rats showed that the rats developed systemic hypertension along with hyperuricemia when administered uricase inhibitor (oxonic acid).[85,86] It proved that this elevated blood pressure was associated with an elevated renin levels and decreased levels of neuronal nitric oxide synthase in the juxta glomerular apparatus which has vasodilatory effect. Prevention of this hypertension may be attained by the addition of ACE inhibitors and L-arginine to a minor extent. It had been proved experimentally that the addition of allopurinol or uricosuric agents such as benziodrone to control the uric acid levels were able to control the elevated blood pressure in experimental models demonstrating the role of uric acid in the development of hypertension and vascular disease.[71]

Obesity

It is known from the studies that leptin levels are increased in insulin resistance associated with metabolic syndrome and type 2 diabetes mellitus (DM). Bedir A et al outlined that leptins are involved in the regulation of serum uric acid levels in humans. They postulated that leptins could provide the link between hyperuricemia and obesity.[87] It is also to be noted that increased free fatty acids and elevated triglycerides were also associated with hyperuricemia independently of body fat distribution and obesity.[88,89]

Hyperglycemia

Uric acid acts as an anti-oxidant at normal serum glucose levels but converts into a pro coagulant during elevated sugar levels known as paradoxical anti-oxidant – pro oxidant switch by urate redox shuttle. This is because hyperglycemia induces both an oxidative and reductive stress on the arterial wall. Oxidative stress by the advanced glycosylation end products and reactive oxygen species ends in glucose auto oxidation leading to pseudohypoxia resulting in the accumulation of NADH and NAD(P)H within the vascular intima.[80,90,91] The naturally occurring local anti-oxidants such as catalyse, SOD or GPX are utilized excessively in these reactions and once these are burnt out, uric acid is free to undergo the paradoxical antioxidant-prooxidant switch in the urate redox shuttle.[92,93]

Homocysteine

In patients with premature atherosclerosis there exist a direct correlation between serum uric acid concentrations and homocysteine concentrations. Both act synergistically, particularly in those thrombotic atherosclerotic plaques which are more prone for rupture due to the depletion of local antioxidants due to increased redox stress.[94-96]

Uric acid and Heart failure

Studies have shown that ischemia in heart failure triggers xanthine oxidase activity which ultimately ends in two products. Firstly, xanthine oxidase is involved in the conversion of hypoxanthine and xanthine to uric acid formation. Secondly, xanthine oxidase ends in the formation of reactive oxygen species and free radicals. Thus serum uric acid levels reflect the circulating xanthine oxidase activity and oxidative stress production in heart failure. There are studies which demonstrate the development of heart failure after myocardial infarction which are associated with hyperuricemia.[97] But, yet, the role of uric acid in coronary artery disease and heart failure has not yet been clear and to be proven strongly. Some studies reported an independent association between uric acid and coronary artery disease, but others found its association only in females.[98] Hence further studies are needed to confirm the association between uric acid levels with heart failure.

Uric acid functions as an antioxidant and probably one of the most important antioxidants in the plasma. Urate scavenges superoxide, hydroxyl radical, and singlet oxygen and chelates transition metals. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide which injures cells by nitrosylating tyrosine residues of proteins and mitochondrial injury. Uric acid may also block this reaction and functions as an anti oxidant.

Uric acid also prevents the degradation of superoxide dismutase, an enzyme critical in maintaining endothelial and vascular functions. Superoxide dismutase 3 is an extracellular enzyme which catalyses the reaction of superoxide anion to hydrogen peroxide thus protecting the cells from free radical injury.[99] The removal of superoxide anion by superoxide dismutase 3 prevents the inactivation of the endothelial vasodilator, nitric oxide. Uric acid thus helps to maintain nitric oxide levels and endothelial function through superoxide dismutase. Normally, superoxide dismutase 3 (SOD 3) is inactivated in the presence of hydrogen peroxide by feedback inhibition. Uric acid blocks this feedback inactivation by hydrogen peroxide by regenerating SOD3 with the production of a urate radical. This latter radical, although potentially a pro-oxidant, has been found to be less reactive than the classic antioxidants and can be rapidly regenerated back to urate in the presence of ascorbate. The increase in serum uric acid levels in subjects with

cardiovascular disease therefore explain that hyperuricemia in heart failure is a compensatory mechanism to counter oxidative stress.

Uric acid may also be responsible for endothelial dysfunction. Studies have reported that uric acid infusion in healthy humans resulted in decremental acetylcholine induced vasodilatation in the forearm thereby highlighting impaired endothelial nitric oxide release. Whereas uric acid is considered as an antioxidant, it also acts as a prooxidant under certain conditions, especially when other antioxidants are low thus explaining the anti coagulant- pro coagulant switch.[99,100]

Studies have shown that free radicals and oxidative stress are involved in the pathophysiology of heart failure. Exponential increase in myocardial oxidative stress in heart failure leads to the development of subcellular abnormalities leading to cardiomyopathic changes, depressed contractile function.[101] The enzyme xanthine oxidase triggered during ischmia in heart failure catalyses the two terminal steps of uric acid synthesis, from hypoxanthine to xanthine and from xanthine to uric acid. These two steps also generate reactive oxygen species and thus uric acid is recognized indirectly as a marker of excess free radicals and reactive oxygen species, playing a key role in the pathogenesis of heart failure.[2]

Serum uric acid appears to increases in patients with congestive heart failure and serves as a valid prognostic biomarker in various studies. Increased

serum uric acid levels are responsible for increased vascular tone and impaired contractility in heart failure through increased xanthine oxidase activity induced free radical stress. Thus uric acid is responsible for metabolic, functional and hemodymanic derangements in heart failure.[102] Experiments are under trial that the drug Oxipurinol, the active metabolite of allopurinol, a potent xanthine oxidase inhibitor, is under research as a newer agent for the treatment of heart failure.[2]

Numerous modern cardiac biomarkers capable of predicting prognosis in heart failure are assessed only by research tests that are not widely available and are expensive. But uric acid being simple, widely available and of low cost serve as a valid prognostic marker for heart failure can be measured anywhere. In heart failure, uric acid levels are reflective of oxidative stress, impaired vasomotor tone, endothelial dysfunction, inflammatory cytokines activation and hyperinsulinemia.[101]The relationship of uric acid with renal function and diuretics increases the value of uric acid as a prognostic marker in heart failure.[103]

The most recognized complication of hyperuricemia is acute and chronic gouty arthritis. Hyperuricemia also causes kidney diseases like nephrolithiasis, urate nephropathy due to deposition of monosodium urate crystals in the renal interstitium and uric acid nephropathy, a reversible cause of acute kidney injury due to deposition of uric acid crystals in collecting ducts, renal pelvis and ureters.

Studies have shown that uric acid is a biomarker of negative prognosis in heart failure of varying severity.[101,104] Uric acid levels are elevated in heart failure and gives accurate prognostic evidence.[3] An ischemic heart induces oxidative stress and xanthine oxidase release due to reduced perfusion, as reflected by hyperuricemia which runs in vicious cycle that is responsible for heart failure pathogenesis.[101,105] Adenosine synthesized in response to hypoxia by ventricular myocardial cells is being broken down to uric acid which enters vascular lumen due to low intracellular pH and negative membrane potential.[106] Xanthine oxidase and uric acid levels are increased in vivo during ischemic conditions and hence elevated uric acid levels are implicated as a marker of tissue ischemia.[107,108] In heart failure, hypoxia caused by transient coronary occlusion causes hyperuricemia.[104]

A Study of tourniquet induced lower limb exsanguinations in patients undergoing surgery shows fivefold exaggerated xanthine oxidase activity and uric acid for atleast two hours.[109] Studies demonstrated urate crystals deposition in the proliferated intima of arterioles and in thrombi which represents the role of uric acid in the pathogenesis of vascular degeneration.[110] Emerging evidences suggest that there is an imbalance between oxidative stress and NO generation in heart failure (nitroso redox imbalance). Xanthine oxidase in the cardiac ventricular myocytes causes pathological hypertrophy and increased apoptosis which impairs

matrix structure. Hence it is proved that not only free radicals but also reduced endothelial NO causes the progression of heart failure. In this situation, xanthine oxidase interacts with NO signaling at various levels including neuronal NO synthase (NOS1) in the sarcoplasmic reticulum. Deficiency or translocation of NOS1 leads to increased xanthine oxidase which in turn impairs excitation contraction coupling and myofilament calcium sensitivity.[111] Free radical induced breakdown of NO can blunt the Frank – starling response in the heart and it may be a mechanism of decreased heart function through hyperuricemia.[112] The following picture depicts the mechanism of hyperuricemia in heart failure. (Fig. 19)

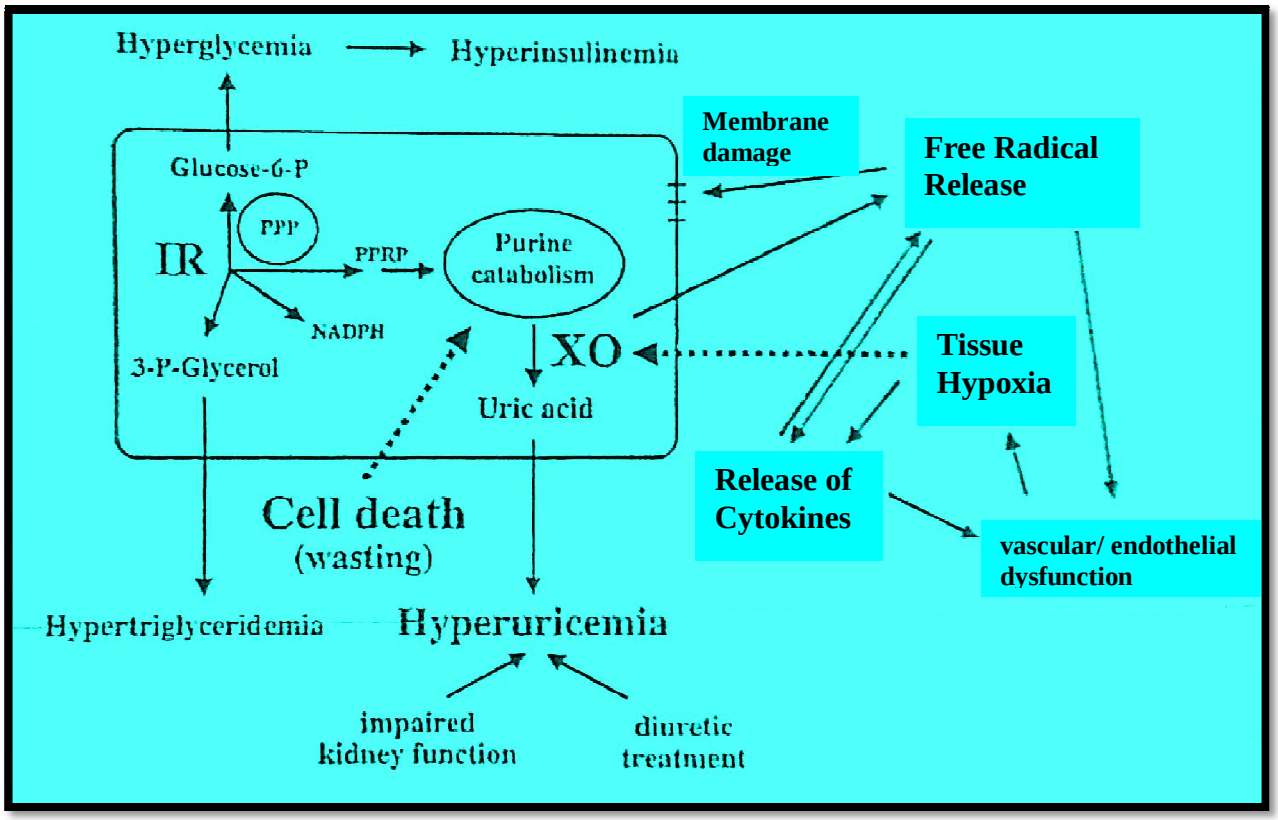


Fig. 19. Mechanism of hyperuricemia in heart failure.

According to the acute coronary syndrome study,[113] there is a close correlation between serum uric acid levels and functional (NYHA) classification in patients with heart failure. Patients with adverse outcomes had hyperuricemia at the initial presentation. Bickel C et al had proven that for every 1 mg/dl increase in uric acid, there is 26% increase in mortality.[114] Sinisa car et al.[115] showed that hyperuricemia was associated with higher in-hospital and 30 days mortality, frequent hospitalizations and reduced life span in heart failure patients.

The LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study had proven that reducing uric acid levels by losartan was associated with beneficial effect on cardiovascular outcome.[116] The uric acid lowering effect of atorvastatin may also have contributed to the decrease in cardio vascular adverse outcomes and mortality in GREASE study (Greek Atorvastatin and Coronary Heart Disease Evaluation Study).[117] Therefore any drugs that lower serum uric acid levels may be beneficial in the treatment of heart failure to reduce oxidative stress and long term mortality. However there are no reports whether uric acid is produced in the failing human heart and whether uric acid levels should be routinely measured in patients with heart failure or long term benefits.

This study has been done to find out whether the serum uric acid levels are elevated in heart failure, to correlate the uric acid levels with ejection fraction, to find its relation with functional class (NYHA classification), to study the association of serum uric acid levels with risk factors for heart failure and to note the prognostic importance of uric acid by relating it with 30 day mortality in heart failure patients.

MATERIALS AND METHODS

MATERIALS & METHODOLOGY

Study Design: Observational Study

Patient selection: 100 patients admitted at Coimbatore Medical College Hospital with Heart Failure during the time period from 1st August 2013 to 31st July 2014.

Inclusion criteria:

- Patients admitted with symptoms and signs of Heart Failure
- Age group of both sexes > 18 years

Exclusion criteria:

- Acute Coronary Syndromes
- Recent myocardial infarction or angina (< 1 month)
- Chronic obstructive pulmonary disease
- Chronic renal failure (Sr. creatinine> 2mg/dl)
- Haematologal malignancies
- Already diagnosed hyperuricemic patients
- Patients on uricosuric drugs

Techniques:

Consent:

The study groups identified by the above criteria (inclusion and exclusion) were first informed about the nature of the study. Participants willing for the study were selected after getting an informed and written consent from

them. Thus, a total of 100 patients were taken up for study who satisfied the inclusion and exclusion criteria. There was no conflict of interest and financial support was Nil.

History and Examination:

Detailed history regarding risk factors, symptoms, signs and aggravating factors of heart failure were recorded and the patients are graded as per NYHA functional classification. Past history of myocardial infarction was also noted. Vital signs were recorded and clinical examinations of all the systems were made.

Serum Uric acid Measurements:

Serum samples for Uric acid measurements were collected within six hours of admission. Serum uric acid levels will be measured with an autoanalyser that uses a phosphotungstic reagent.

Reference Values for Serum Uric acid levels:

In Men: 3.5 - 7.0 mg/dL

In Women: 2.5 - 6.0 mg/dL

Hyperuricemia is defined as serum uric acid levels >7 mg/dL in males and >6 mg/dL in females.

Electrocardiogram:

Electrocardiogram was performed for all patients to rule out acute coronary syndromes and to identify previous Myocardial Infarction. The QRS duration in all the patients was measured and compared with serum uric acid levels.

Echocardiogram:

Echocardiogram was performed in all patients included in the study to assess the degree of cardiac dysfunction (LV ejection fraction) and to identify previous myocardial infarction.

Patient Short Term Outcome:

All patients included in the study were followed up for a period of one month to assess the mortality rate after one month and re hospitalization within one month.

Statistical Analysis:

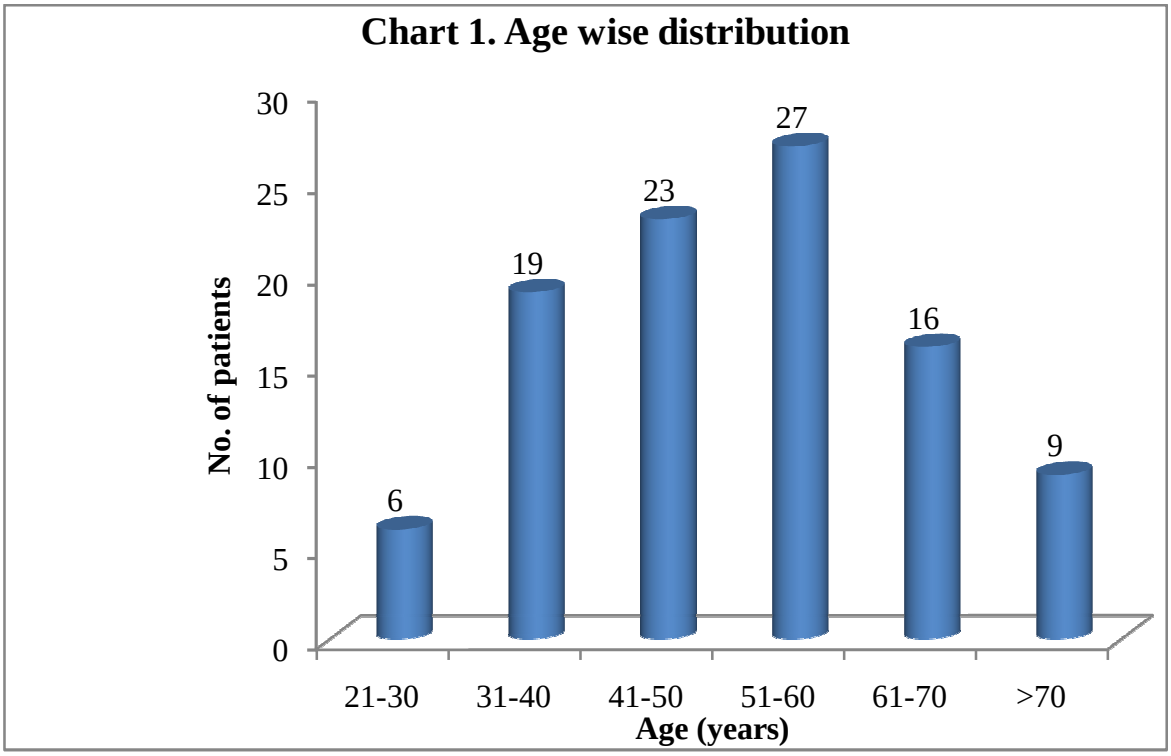
Data was entered in Microsoft excel spread sheet and analyzed statistically using SPSS 20.0 software package. Significance testing of the difference between means was done by unpaired 2 tailed student ‘t’- test for independent samples, and correlations were estimated by Pearson coefficient. Significance was considered, if the ‘p’ value was below 0.05.

RESULTS

RESULTS:

TABLE 1. AGE WISE DISTRIBUTION

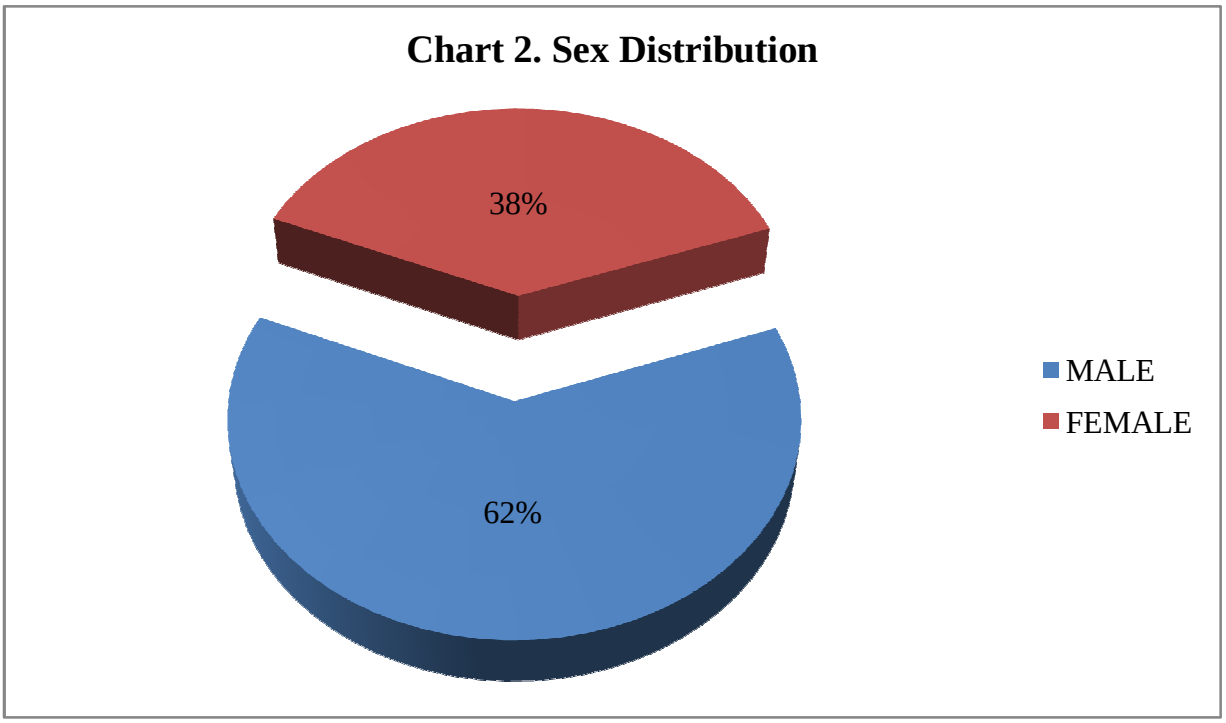
Age category (years)	No. of patients (n=100)
21-30	6
31-40	19
41-50	23
51-60	27
61-70	16
>70	9



In this study of 100 patients, majority of the patients were in fourth and sixth decades.

TABLE 2. SEX DISTRIBUTION

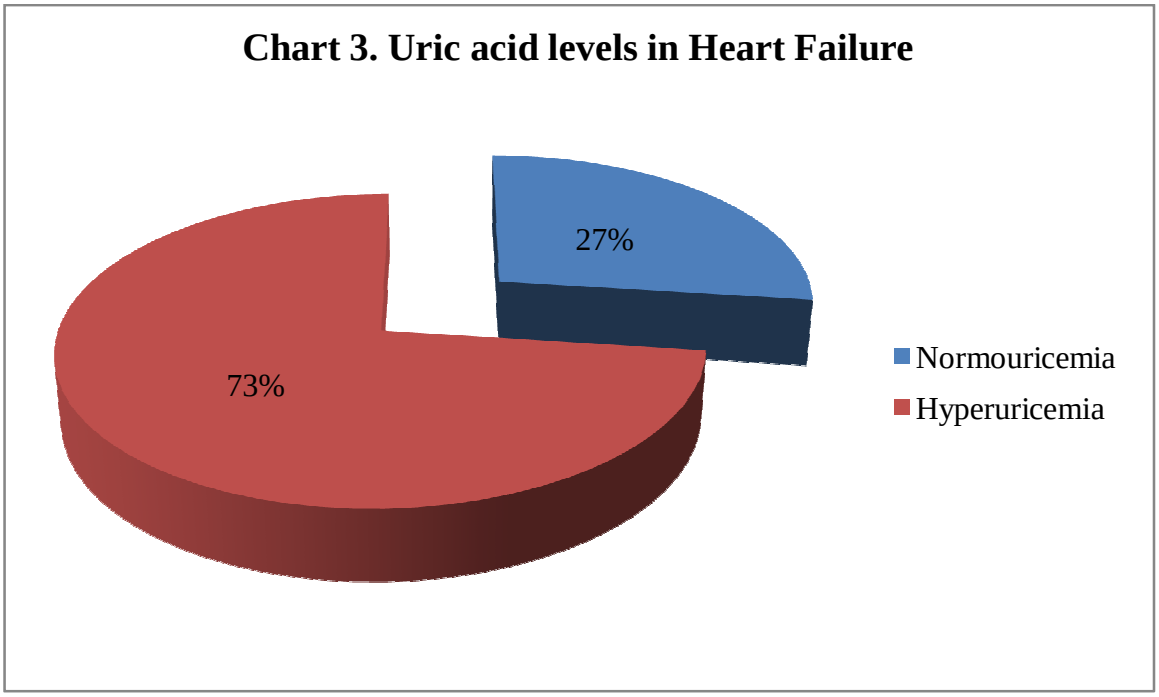
Sex	No. of patients (n=100)
Male	62
Female	38



In the study group, majority of the patients were males comprising about 62% and females about 38%.

TABLE 3. URIC ACID LEVELS IN HEART FAILURE

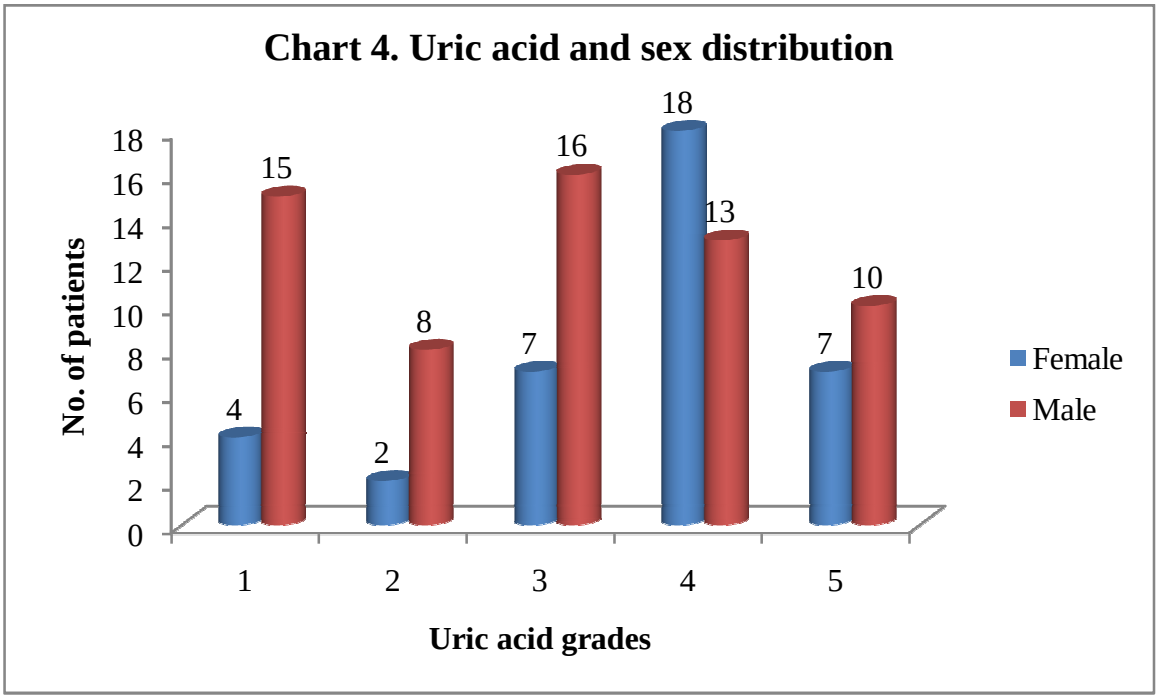
Normouricemia	Hyperuricemia
27%	73%



This study proves that serum uric acid levels were elevated in heart failure with results showing that majority 73% had hyperuricemia and minority 27% had normal uric acid levels.

TABLE 4. URIC ACID AND SEX DISTRIBUTION

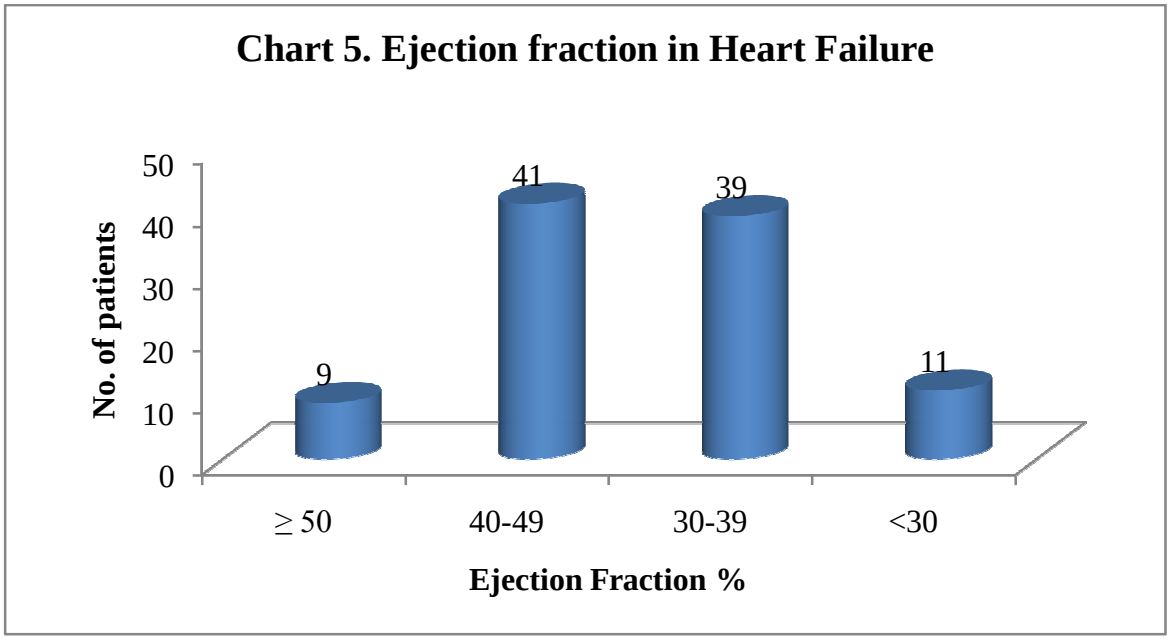
Sex	Uric Acid (mg/dl)					TOTAL
	≤6	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Female	4	2	7	18	7	38
Male	15	8	16	13	10	62
Total	19	10	23	31	17	100



In this study, out of 32 females, 34 had hyperuricemia and only 4 had normouricemia. And out of 68 males, 39 had hyperuricemia and 29 had normal uric acid levels showing that prevalence of hyperuricemia was greater in females compared to males.

TABLE 5. EJECTION FRACTION IN HEART FAILURE

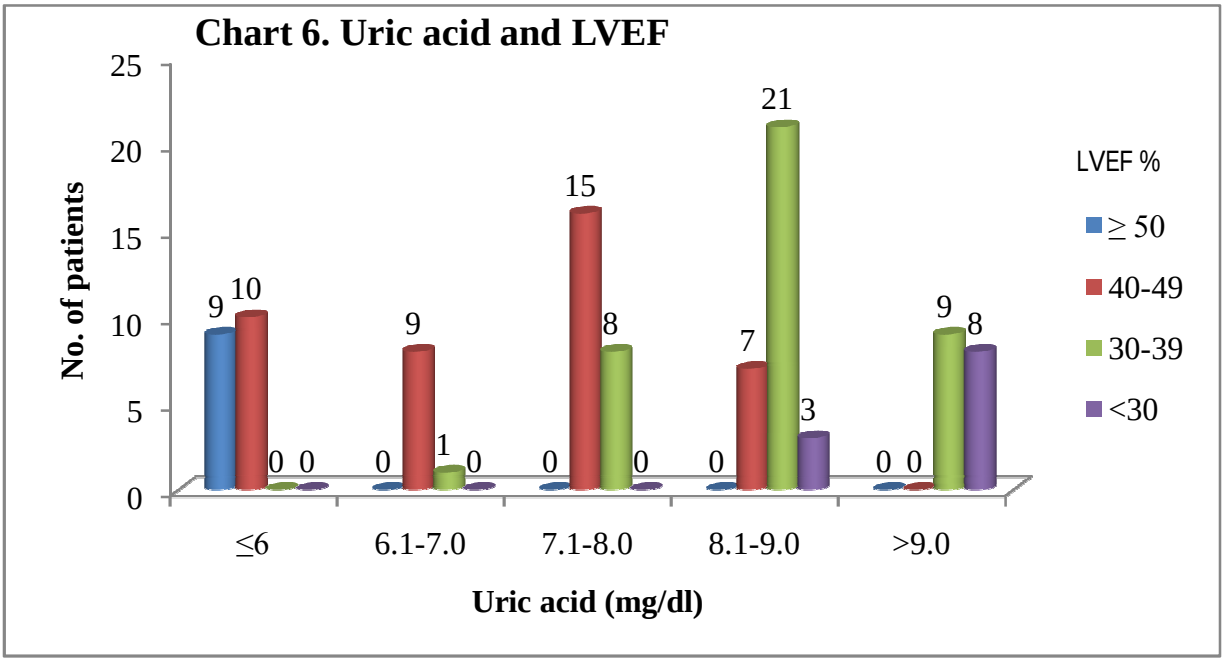
LVEF %	No. of patients
≥50	9
40-49	41
30-39	39
<30	11



Majority of the patients with heart failure in this study had ejection fraction in the range of 30 % – 49 % with 41 people in the EF range of 40 – 49 % and 39 people in the EF range of 30 – 39 %.

TABLE 6. URIC ACID AND LVEF

LVEF %	Uric Acid (mg/dl)					p value	Pearson Correlation Coefficient
	≤6	6.1-7.0	7.1-8.0	8.1-9.0	>9.0		
≥50	9	0	0	0	0	< 0.01	- 0.853
40-49	10	9	15	7	0		
30-39	0	1	8	21	9		
<30	0	0	0	3	8		

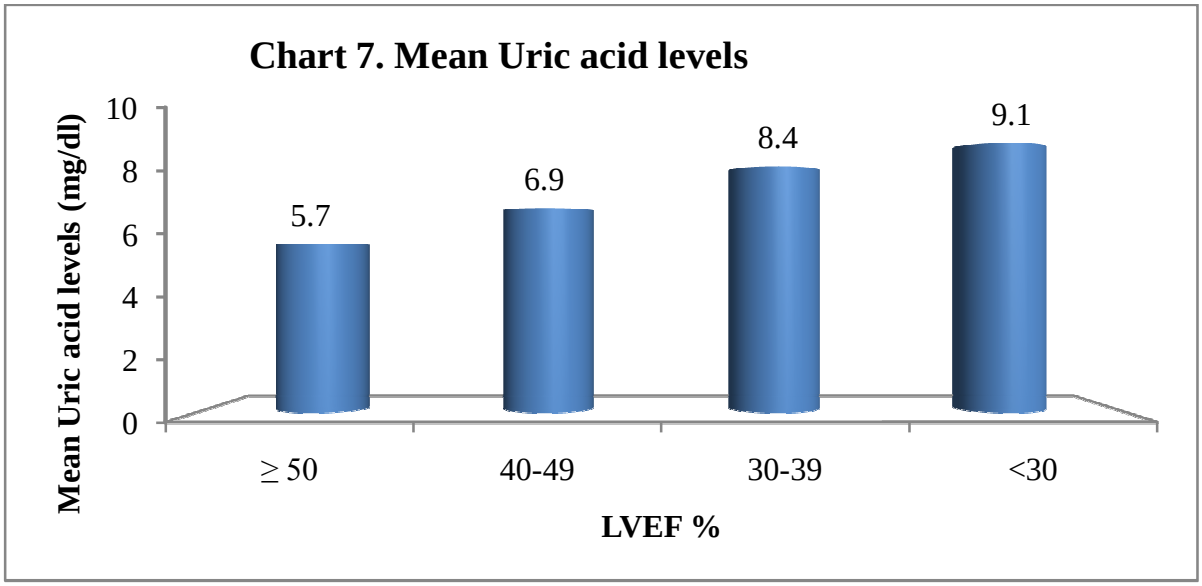


The serum UA levels were compared with various grades of LVEF. In patients with decreased ejection fraction, all the patients (100%) had significant rise in serum UA. As the ejection fraction increased, the number of patients with

elevated serum uric acid levels proportionately decreased (0% in patients with EF>50). This association holds good with a P value of <0.01 and Pearson correlation coefficient of – 0.853. Thus this study shows that elevated uric acid levels had negative correlation with ejection fraction proving that progressive hyperuricemia indicates cardiac dysfunction in heart failure.

TABLE 7. MEAN URIC ACID LEVELS AND LVEF

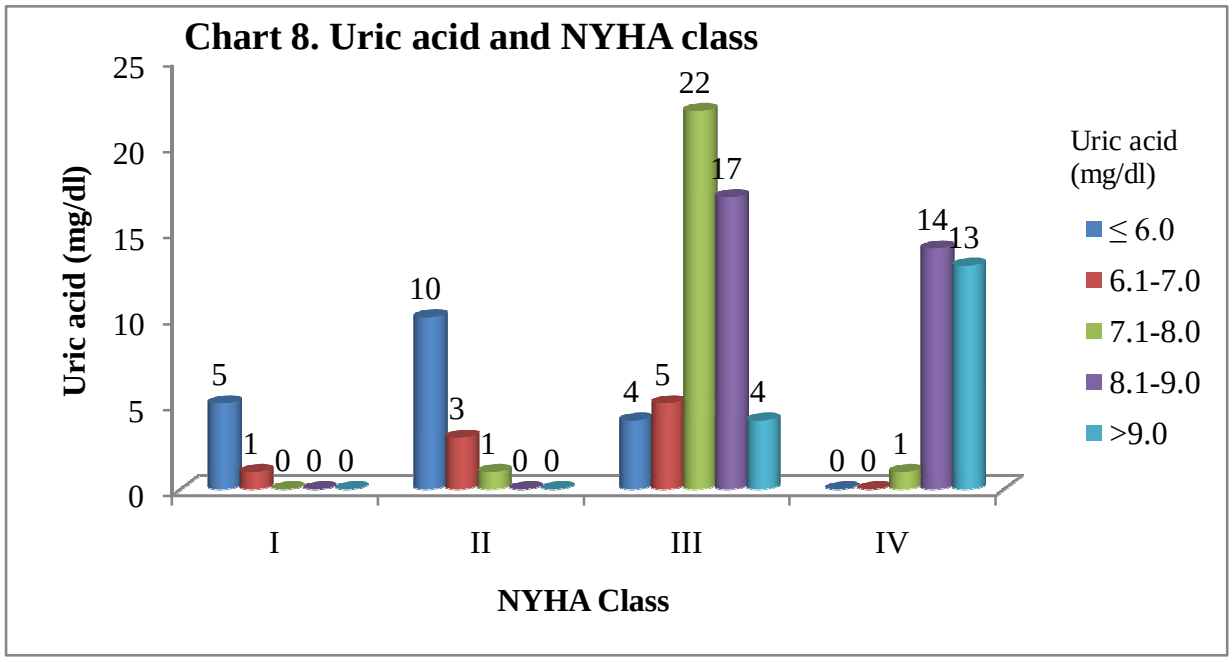
LVEF %	Mean Uric acid levels (mg/dl)
≥50	5.7
40-49	6.9
30-39	8.4
<30	9.1



The mean UA levels of patients with different ejection fractions were compared. There was significant rise of serum UA levels in patients with reduced ejection fraction. The mean UA levels of patients with LVEF of >50%, 40-49%, 50-59% and <30% are 5.7, 6.9, 8.4 and 9.1 mg/dL respectively. These results also show that serum uric acid levels correlate negatively with ejection fraction in heart failure.

TABLE 8. URIC ACID AND NYHA CLASS

Uric acid	NYHA Class				p value
	I	II	III	IV	
≤6	5	10	3	1	< 0.01
6.1-7.0	1	3	6	0	
7.1-8.0	0	1	21	1	
8.1-9.0	0	0	17	14	
>9.0	0	0	4	13	
Total	6	14	51	29	

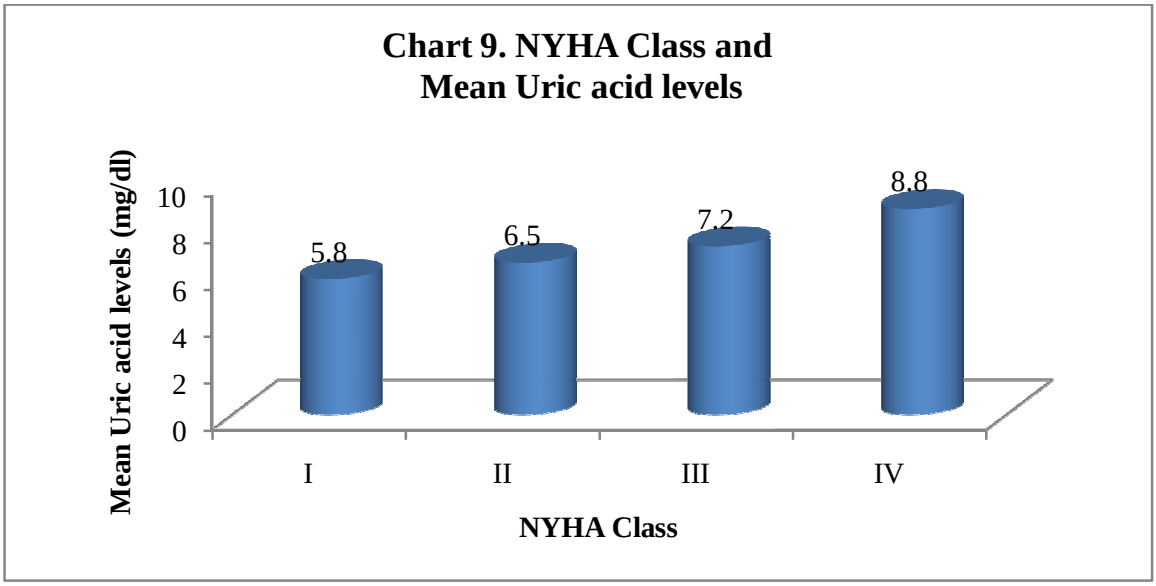


The serum UA levels were compared with various grades of NYHA functional class in HF. In patients with grade III and IV NYHA, majority had significant rise in serum UA. As the NYHA fuctional class increases, the number of patients with elevated serum uric acid levels proportionately increases. This

association holds good with a P value of <0.01. Thus this study shows that elevated uric acid levels had positive correlation with NYHA functional class proving that hyperuricemia indicates progression of the disease in heart failure.

TABLE 9. NYHA CLASS AND MEAN URIC ACID LEVELS

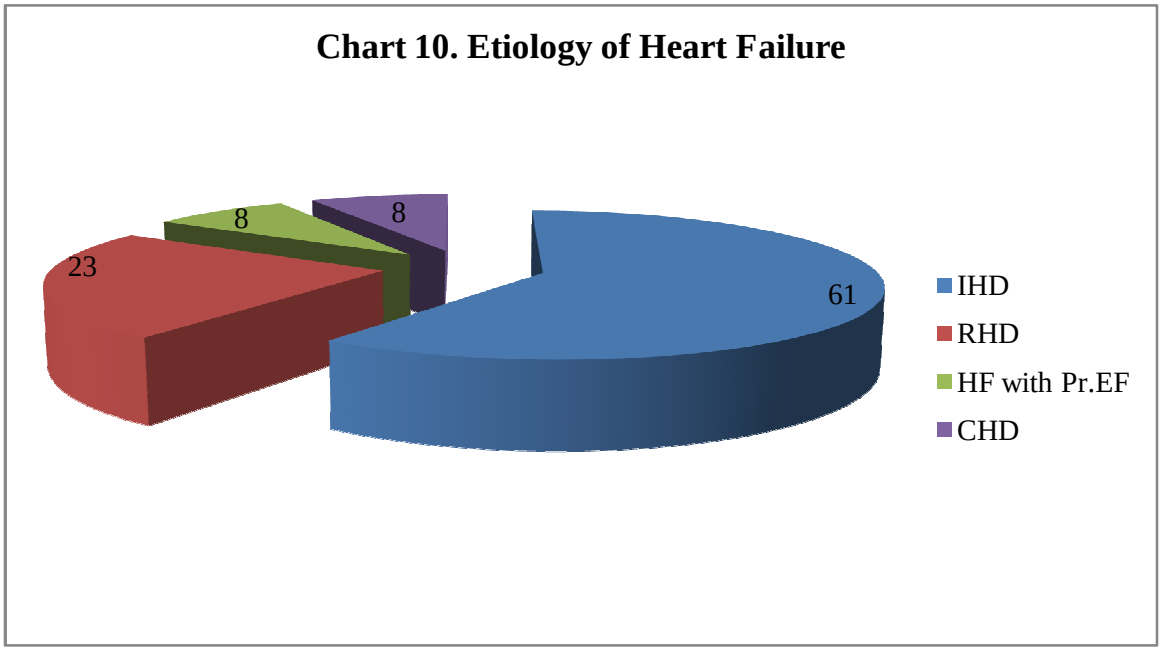
NYHA Class	Mean Uric acid levels (mg/dl)
I	5.8
II	6.5
III	7.2
IV	8.8



The mean UA levels of patients with different NYHA functional class were compared. There was a progressive rise of serum UA levels from grade I to grade IV NYHA functional class in HF patients. The mean UA levels of patients with NYHA grade I, II, III and IV are 5.8, 6.5, 7.2 and 8.8 mg/dL respectively. These results prove that serum uric acid levels correlate positively with NYHA functional class in heart failure.

TABLE 10. ETIOLOGY OF HEART FAILURE

Etiology	No. of patients
Ischaemic Heart Disease	61
Rheumatic Heart Disease	23
Heart Failure with Preserved EF	8
Congenital Heart Disease	8



In the study, majority (61%) had ischemic cardiomyopathy as the cause of HF, with Rheumatic heart disease comprising about 23 %.

TABLE 11. URIC ACID IN ACUTE AND CHRONIC HEART FAILURE

Uric acid (mg/dl)	Acute Heart Failure	Chronic Heart Failure	p value
≤6	1	18	< 0.01
6.1-7.0	0	10	
7.1-8.0	2	21	
8.1-9.0	17	14	
>9.0	15	2	
Total	35	65	

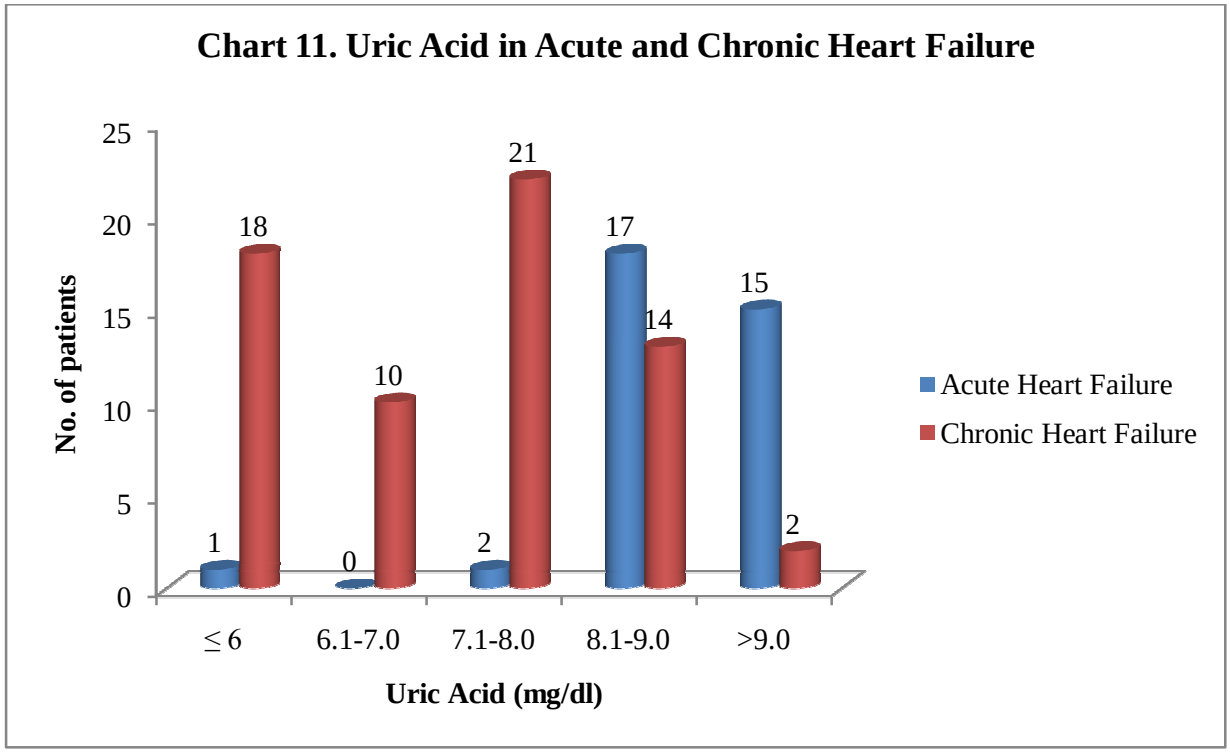
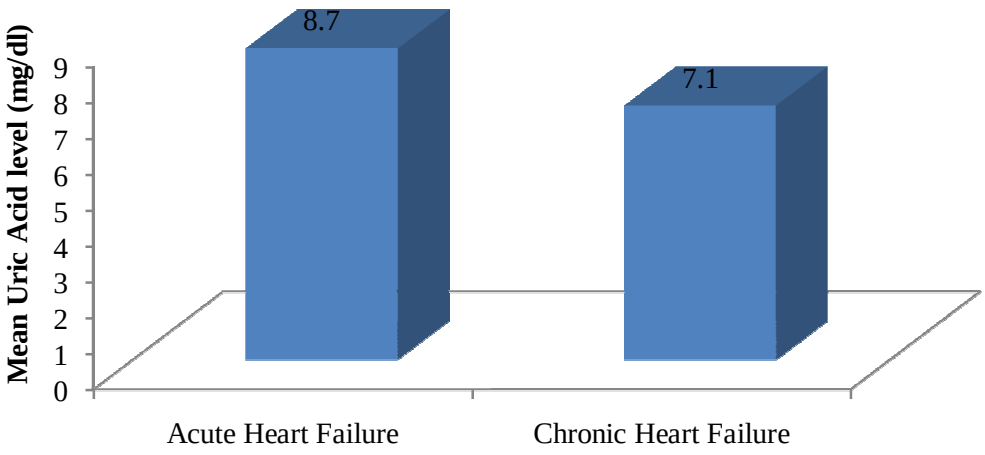


TABLE 12. MEAN URIC ACID LEVELS IN ACUTE AND CHRONIC HEART FAILURE

	Mean Uric Acid levels (mg/dl)
Acute Heart Failure	8.7
Chronic Heart Failure	7.1

Chart 12. Mean Uric Acid levels in Acute and Chronic Heart Failure



Mean uric acid levels were higher in acute decompensated heart failure than chronic HF showing the significant association of p value < 0.01.

TABLE 13. RISK FACTORS ASSOCIATED WITH HEART FAILURE

Risk Factors	Percentage (%)
Dyslipidemia	53
Hypertension	47
Smoking	47
Diabetes Mellitus	44
Alcohol	41

Chart 13. Risk Factors and Heart Failure

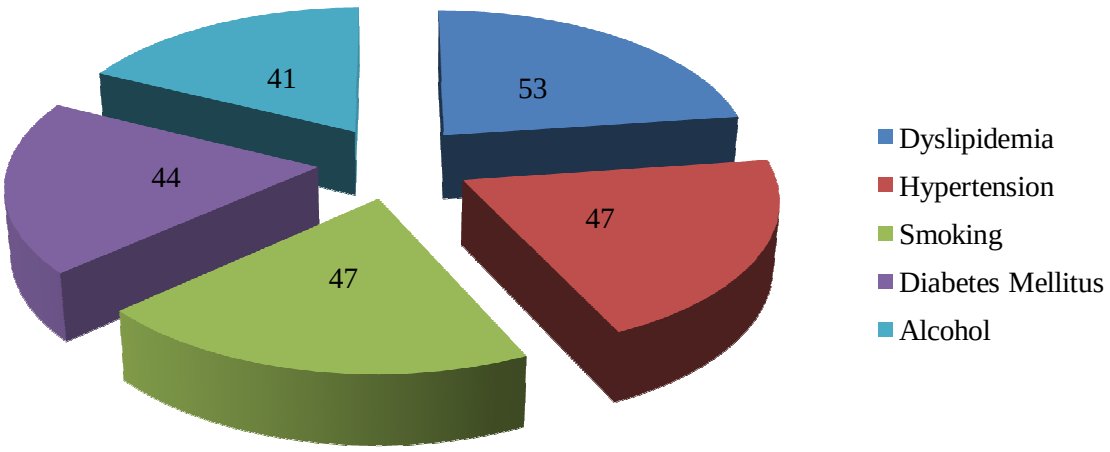
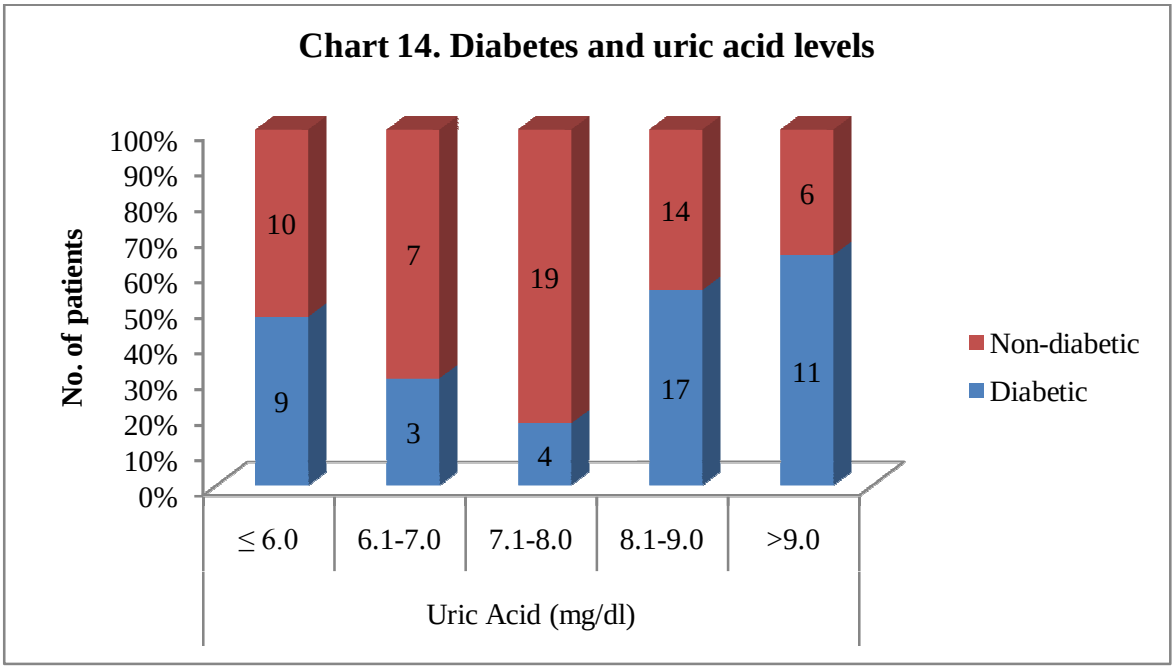


TABLE 14. DIABETES AND URIC ACID LEVELS

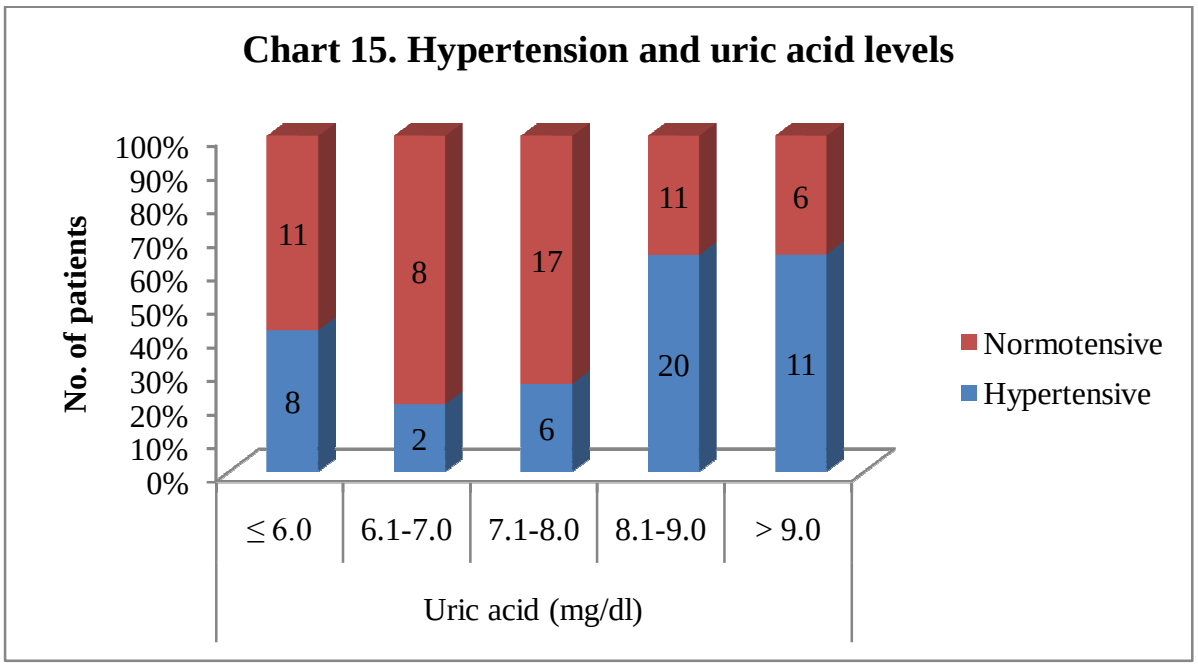
Diabetes Mellitus	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Diabetic	9	3	4	17	11	<0.01
Non-diabetic	10	7	19	14	6	



Serum UA were compared in both diabetic and non-diabetic individuals.The correlation had a p value of <0.01, which is significant showing that hyperuricemia is associated with impaired glucose tolerance in patients with diabetes.

TABLE 15. HYPERTENSION AND URIC ACID LEVELS

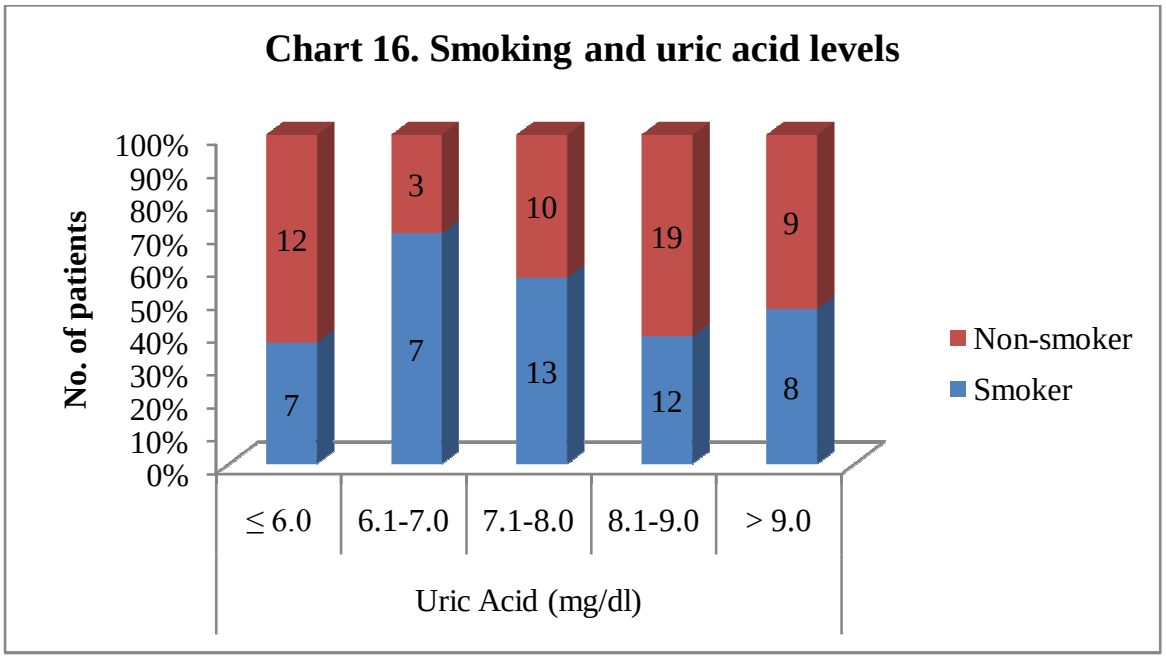
Hypertension	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Hypertensive	8	2	6	20	11	<0.01
Normotensive	11	8	17	11	6	



Serum UA levels were compared in both hypertensive and normotensive individuals. The correlation had a p value of <0.01, which is significant showing that hyperuricemia is associated with hypertension.

TABLE 16. SMOKING AND URIC ACID LEVELS

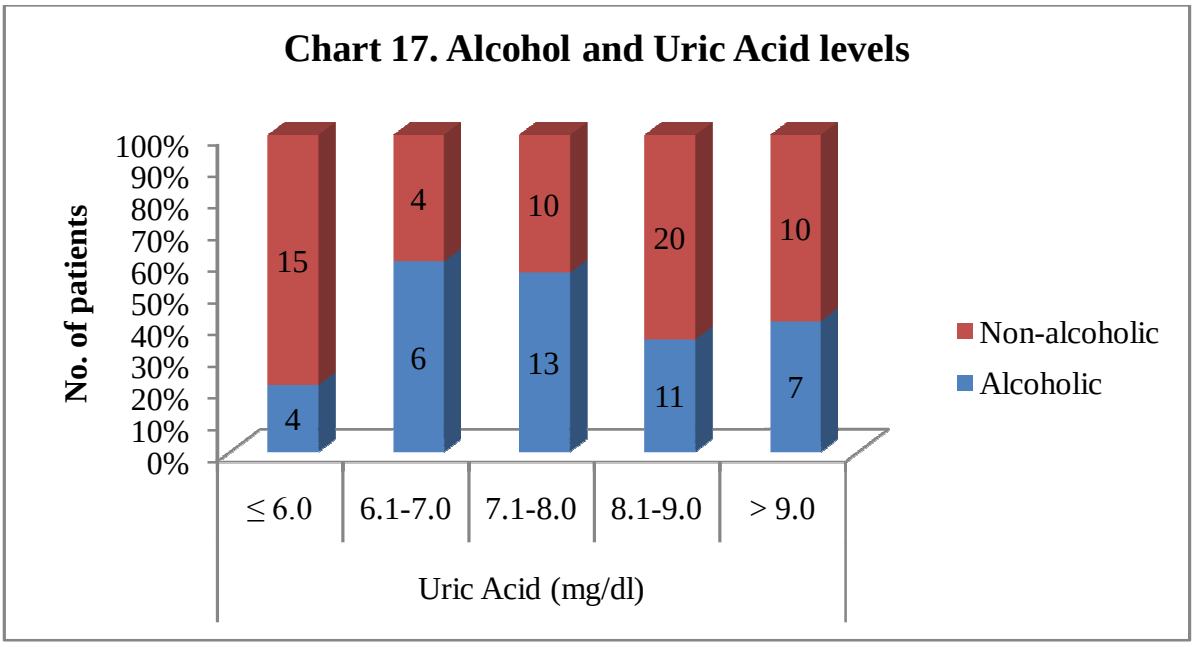
Smoking	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Smoker	7	7	13	12	8	0.330
Non-smoker	12	3	10	19	9	



Serum UA levels were compared in both smokers and non smokers. The correlation had a p value of 0.330, which is insignificant.

TABLE 17. ALCOHOL AND URIC ACID LEVELS

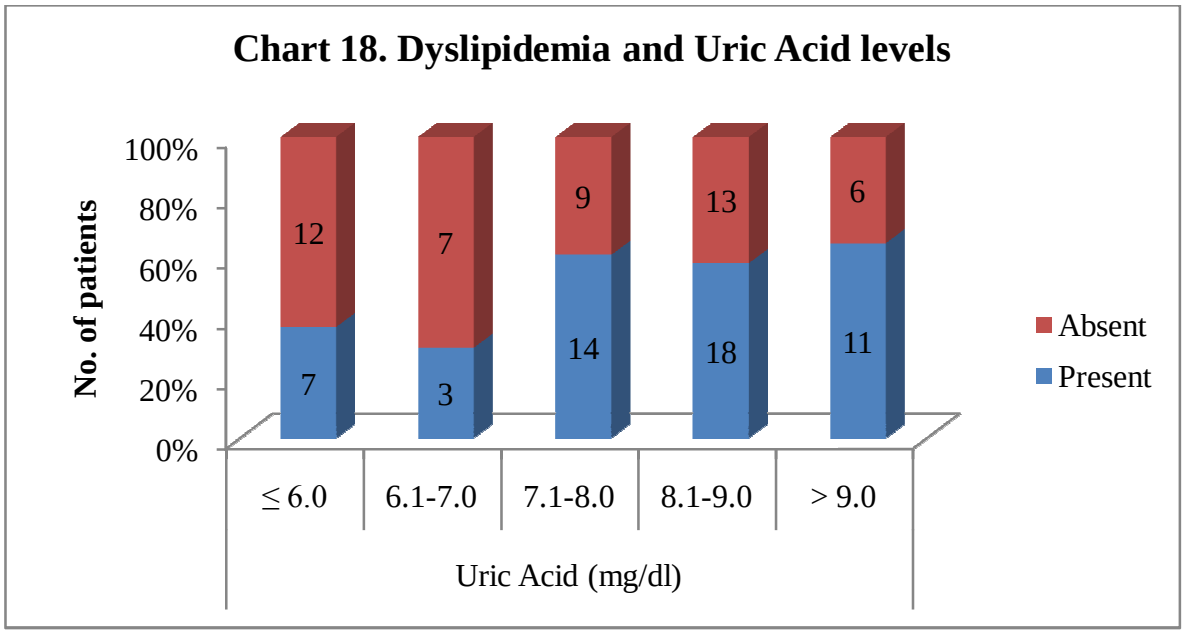
Alcohol	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Alcoholic	4	6	13	11	7	0.121
Non-alcoholic	15	4	10	20	10	



Serum UA levels were compared in both alcoholics and non alcoholics. The correlation had a p value of 0.121, which is insignificant.

TABLE 18. DYSLIPIDEMIA AND URIC ACID LEVELS

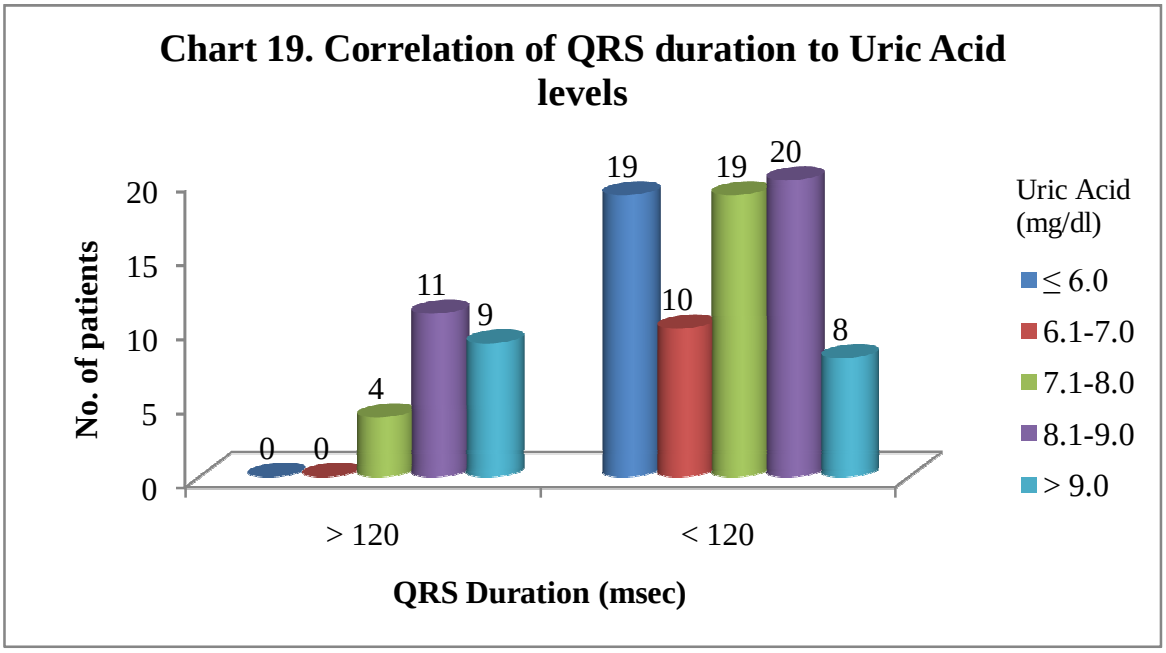
Dyslipidemia	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Present	7	3	14	18	11	0.204
Absent	12	7	9	13	6	



Serum UA levels were compared in patients with normal lipid profile and dyslipidemia. The correlation had a P value of 0.204, which is insignificant.

TABLE 19. CORRELATION OF QRS DURATION (ECG) TO URIC ACID LEVELS

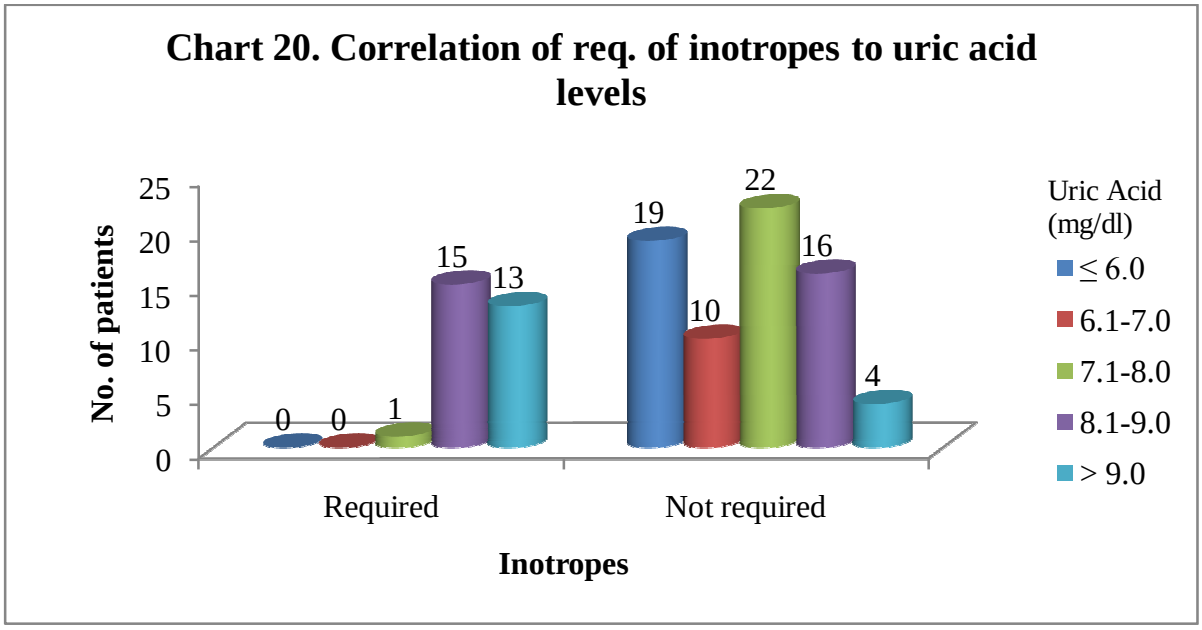
QRS Duration (msec)	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
> 120	0	0	4	11	9	<0.001
< 120	19	10	19	20	8	



In the study, serum uric acid levels were compared with QRS duration of >120 msec and < 120 msec. All patients (100%) with QRS > 120 msec had elevated UA levels. The correlation had a p value < 0.001 which is significant.

TABLE 20. CORRELATION OF REQUIREMENT OF INOTROPES TO URIC ACID LEVELS

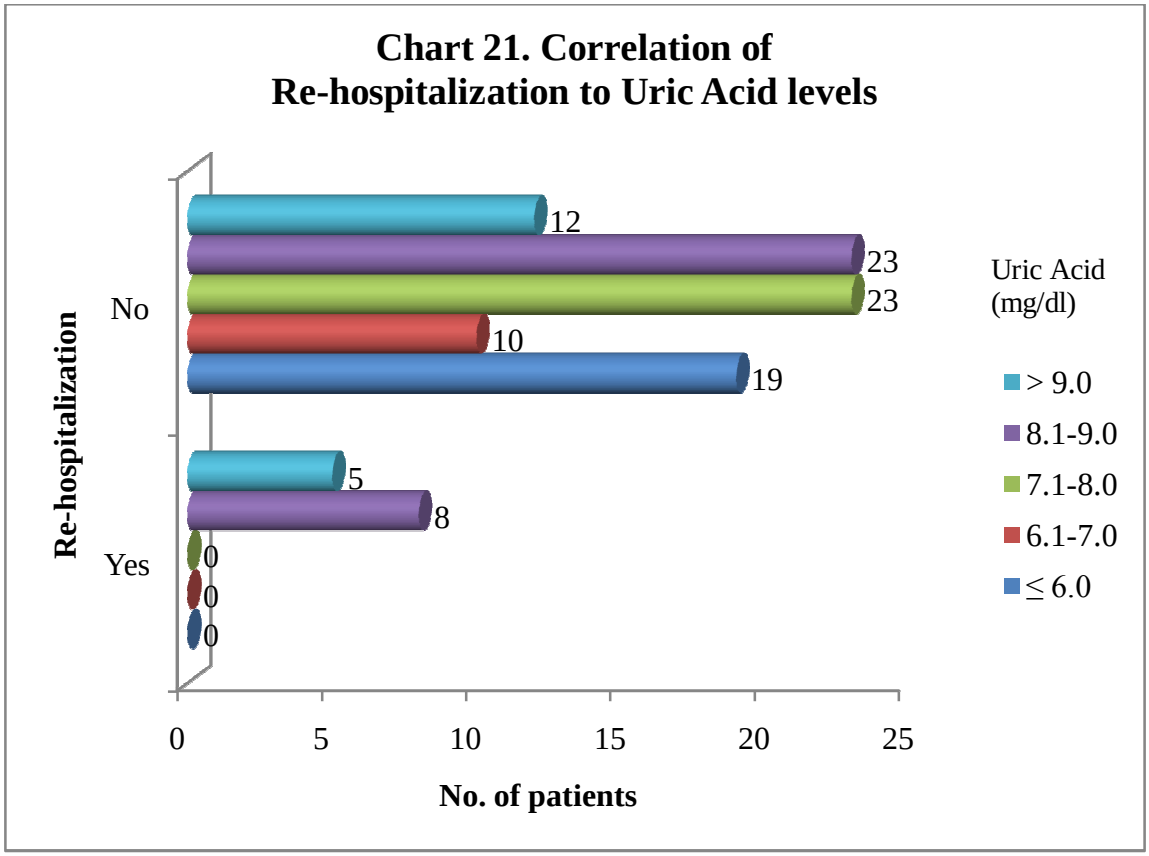
Inotropes	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Required	0	0	1	15	13	< 0.001
Not Required	19	10	22	16	4	



In the study, serum uric acid levels were compared with patients who required inotropic supports and those who do not. All patients (100%) who required inotropes had elevated UA levels. The correlation had a p value < 0.001 which is significant.

TABLE 21. CORRELATION OF RE-HOSPITALIZATION TO URIC ACID LEVELS

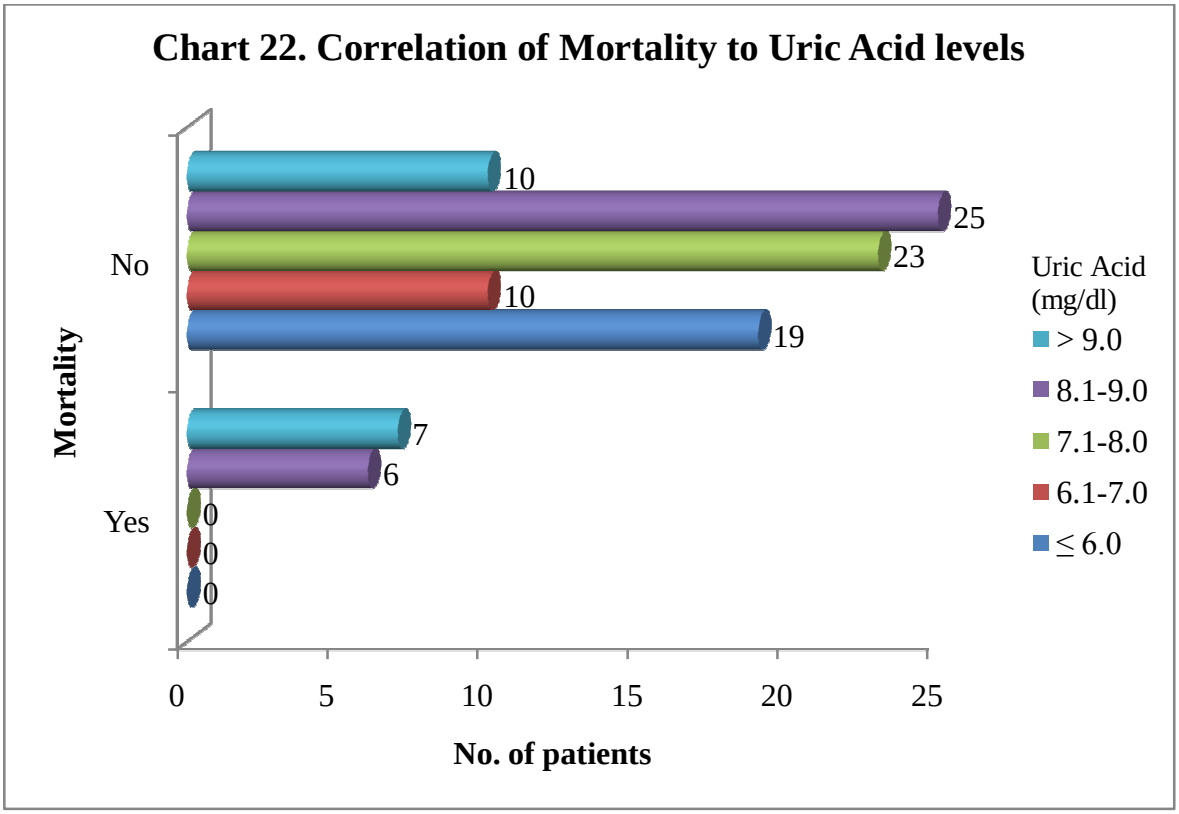
Re-hospitalization	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Yes	0	0	0	8	5	<0.003
No	19	10	23	23	12	



In the study, serum uric acid levels were compared with patients with rehospitalisation rates within one month. All patients (100%) who were rehospitalised had elevated UA levels. The correlation had a p value < 0.003 which is significant.

TABLE 22. CORRELATION OF MORTALITY TO URIC ACID LEVELS

Mortality	Uric Acid (mg/dl)					p value
	≤6.0	6.1-7.0	7.1-8.0	8.1-9.0	>9.0	
Yes	0	0	0	6	7	< 0.001
No	19	10	23	25	10	

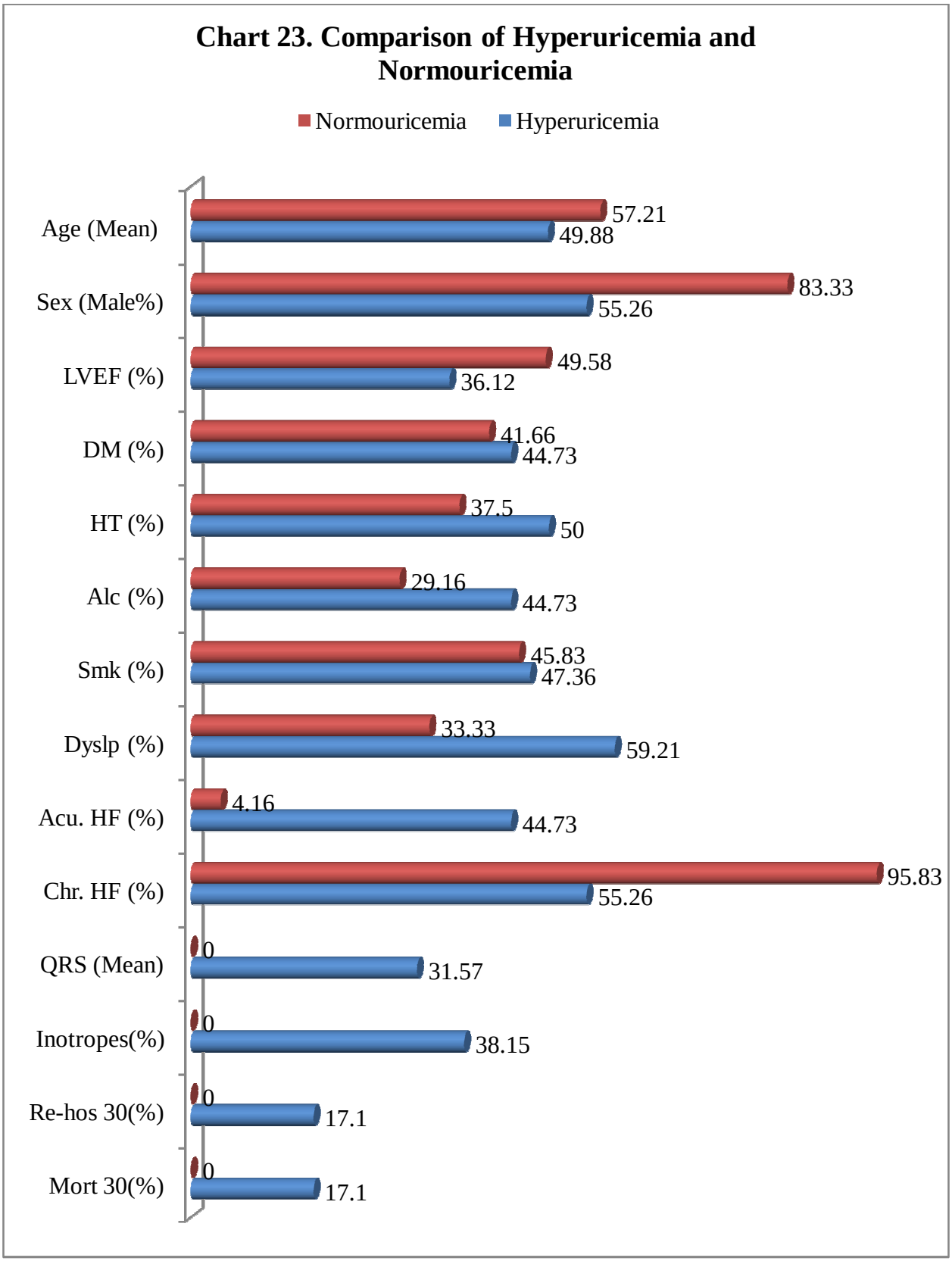


In the study, serum uric acid levels were compared with 30 day mortality rate. All patients (100%) who died within one month had elevated UA levels. The correlation had a p value < 0.001 which is significant.

TABLE 23. COMPARISON OF FEATURES BETWEEN HYPERURICEMIA AND NORMOURICEMIA

Factors	Hyperuricemia	Normouricemia
Age (Mean)	49.88	57.21
Sex (Male %)	55.26	83.33
LV Ejection Fraction (%)	36.12	49.58
Diabetes (%)	44.73	41.66
Hypertension (%)	50	37.5
Alcohol (%)	44.73	29.16
Smoking (%)	47.36	45.83
Dyslipidemia (%)	59.21	33.33
Acute heart failure (%)	44.73	4.16
Chronic heart failure (%)	55.26	95.83
QRS duration (Mean)	31.57	0
Inotropes required (%)	38.15	0
Re-hospitalization at 30 days (%)	17.1	0
Mortality at 30 days (%)	17.1	0

Chart 23. Comparison of Hyperuricemia and Normouricemia



DISCUSSION

DISCUSSION

Natriuretic peptides have been the established biomarkers for the risk stratification of patients with heart failure. Previous studies show that serum uric acid may also function as a prognostic risk marker in HF patients. BNP increases as an adaptive response due to increased ventricular filling pressures, whereas uric acid levels are increased in HF as a maladaptive response of increased xanthine oxidase activity reflecting increased vascular tone and impaired cardiac contractility. In this study, the diagnostic and prognostic implications of serum UA have been studied in a population comprising 100 patients, who were admitted with symptoms and signs of heart failure syndromes. These patients were assessed clinically on admission and serum UA measured within 6 hours of admission, followed by laboratory and echocardiographic evaluation.

This study shows that hyperuricemia is found in majority (73%) of heart failure patients with increased prevalence in females compared to males which is in concurrence with the research studies by Michelle and Uzma et.al in 2009. Serum uric acid levels are increased markedly in acute decompensation than chronic heart failure. Pascual and figal in 2007 shows that hyperuricemia is more common in acute heart failure syndromes than chronic state and majority of the patients with hyperuricemia in acute decompensation shows severe clinical

impairment. Increased uric acid levels in acute HF indicates increased oxidative stress and xanthine oxidase activity causing adverse left ventricular remodeling. Endothelial dysfunction and hypoxia causes exaggerated xanthine oxidase activity producing hyperuricemia in heart failure, which is further augmented by the impaired kidney function and use of diuretics in heart failure.

Left ventricular ejection fraction and NYHA functional class were taken as the markers for the severity of heart failure. The study shows that in patients with decreased ejection fraction, all the patients (100%) had significant rise in serum UA. As the ejection fraction increased, the number of patients with elevated serum uric acid levels proportionately decreased (0% in patients with EF>50). This association holds good with a p value of <0.01. Thus this study shows that elevated uric acid levels had negative correlation with ejection fraction proving that progressive hyperuricemia indicates cardiac dysfunction in heart failure.

The severity of heart failure was compared with the severity of uric acid rise, which showed progressive decrease in ejection fraction with increasing uric acid values. This association was statistically significant. The mean uric acid values also increased with decreasing ejection fraction. The mean ejection fraction in patients with hyperuricemia and normal uric acid levels are 36% and 49%

respectively. Hence, serum uric levels can be used as a qualitative marker for assessing the severity of heart failure. These results were confirmative of the research done by Pinelli and Hiroshi et. al in 2007.

The serum UA levels were compared with various grades of NYHA functional class in HF. In patients with grade III and IV NYHA, majority had significant rise in serum UA. As the NYHA functional class increases, the number of patients with elevated serum uric acid levels proportionately increases. There was a progressive rise of serum UA levels from grade I to grade IV NYHA functional class in HF patients. This association holds good with a p value of <0.01. Thus this study shows that elevated uric acid levels had positive correlation with NYHA functional class proving that hyperuricemia indicates progression of the disease in heart failure which is similar to the studies done by Domingo. et. al in 2007 and Murtaza. et. al in 2009.

Risk factors associated with heart failure were diabetes, hypertension, smoking, alcohol and dyslipidemia. All these risk factors were individually studied and compared with normouricemic and hyperuricemic group of patients. Studies of Uzma et. al in 2009 and Yoo et al.in 2005 have demonstrated that serum uric acid concentration was shown to independently correlate with hypertension. In our

study there was significant association between hyperuricemia and hypertension as evident by p value < 0.01. Hyperuricemia per se stimulate vascular remodeling and smooth musle proliferation causing hypertension. Thus this study shows that hyperuricemia is independently linked with hypertension irrespective of the etiology of heart failure.

Studies by Yoo et. al in 2005 and Becker and Jolly in 2006 showed that hyperuricemia was clearly related to hyperglycemia. In our present study we found there was a significant correlation between hyperuricemia and diabetes with p value < 0.01. Insulin resistance, hyperinsulinemia and tissue wasting in diabetes accelerated the catabolism of purines leading to hyperuricemia. Cappuccio and colleagues showed that hyperuricemia is associated with increased renal sodium reabsorption thus linking increased uric acid levels with hypertension and hyperinsulinemia. Thus this study shows that increased uric acid levels are associated with diabetes significantly irrespective of the etiology of heart failure.

Studies done by Uzma et.al.in 2009 shows that hyperuricemia was not independently associated with hyperlipidemia. This study also shows similar results that hyperuricemia had no correlation with hyperlipidemia with a p value of 0.204. Further alcohol use and smoking also had no correlation with hyperuricemia with p value of 0.330 and 0.121 respectively.

The relevant hemodynamic characteristics of normouricemic and hyperuricemic heart failure patients were compared. These include QRS duration in ECG, and requirement of ionotropes. It was found that patients with elevated uric acid levels were associated with impaired haemodynamics in the form of increased incidence of hypotension. Hyperuricemic patients had wider QRS complexes suggesting increased atrio ventricular dysynchrony and were associated with increased requirement for ionotropes during the initial management. The association was statistically significant with the p value < 0.001 which is in concurrence with the results of Anker and Stefan et.al in 2009.

The prognosis of patients was assessed by means of 30 day mortality rate and rehospitalization rates within one month. It was found that patients with higher serum uric acid levels were associated with increased rates of rehospitalization and increased mortality rate. The association was statistically significant with a p value of < 0.001. Adriana and Danielle et. al in 2008 also proved the same association.

From the above findings, it is made clear that elevated uric acid levels serves as a clinical marker for the multiple pathological processes in the progression of heart failure and reduction in xanthine oxidase activity improves cardiac contractility, reduces oxidative stress, limits infarct size, inflammation and

platelet adhesiveness. All these effects would be protective to patients with heart failure and suggests a hypothesis that xanthine oxidase inhibitors may act as novel drugs in the management of cardiac failure in future.

This study had certain limitations. Results could have been more accurate by increasing the sample size. The patients were followed up only for 1 month and by increasing the duration of follow up by 6 months to 1 year would have achieved better assessment of differences in the results.

CONCLUSION

CONCLUSION

To conclude, the prevalence of hyperuricemia was found to be significantly higher in patients with cardiac failure and the severity of UA rise had a high correlation to the severity of heart failure. Hyperuricemia is more common in acute decompensated heart failure than chronic heart failure patients. Elevated serum uric acid levels correlate inversely with ejection fraction suggesting that progressive hyperuricemia in cardiac failure indicates deteriorating cardiac function. Patients with elevated serum UA levels were associated with poorer NYHA functional class proving that hyperuricemia predicts the severity of cardiac failure. Hyperuricemic patients were associated with adverse clinical and biochemical features compared to normouricemic patients in the form of increased QRS duration and inotropic requirements. Serum uric acid levels were increased in diabetes and hypertension and had an independent association, irrespective of the etiology of heart failure. Patients with higher uric acid levels were associated with adverse outcomes and poor prognosis in the form of increased rehospitalization rates and 30 day mortality rates.

SUMMARY

SUMMARY

The study was initiated in order to determine the prognostic significance of serum uric acid levels in heart failure syndromes and its correlation with ejection fraction.

The study was conducted in Coimbatore medical college hospital, Coimbatore, which included 100 patients who were admitted with features of heart failure. Patients, who satisfied the criteria for inclusion, were subjected to basic blood investigations and serum uric acid levels were measured in them. Echocardiography was done in all the patients to assess the severity of heart failure. The patients were followed up for a period of one month to determine the mortality and adverse outcomes.

Results from the study showed that serum uric acid levels were significantly raised in heart failure. Increased serum uric acid levels in heart failure correlates negatively with ejection fraction and positivey with NYHA functional class, thus predicting the prognosis and severity. Hyperuricemia is independently associated with hypertension and diabetes, irrespective of the etiology of cardiac failure. Increased serum uric acid levels were also associated with adverse outcomes in terms of rehospitalisation rates and mortality.

Thus, it is evident from this study that high serum uric acid levels could be a strong and valid biomarker of impaired prognosis and mortality in patients with cardiac failure, predicting the severity and hemodynamic derangements. The measurement of serum uric acid levels is simple and widely available at low cost. Hence routine measurement of serum uric acid levels in assessing the cardiovascular risks may contribute to the improved ability to stratify risk in cardiac failure.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular Risk. N.Eng.J.Med.2008;359:1811-1821
2. Uzma Bano, Murtaza Gondal, Dawar Majeed. High serum uric acid levels as a marker of poor cardiovascular outcome and high mortality. JPMI. 2009; 23(1): 22-27
3. Mann DL, Chakinala M. Heart Failure and Cor Pulmonale. In: Longo DL, Kasper DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 18th edition. United States of America. Mac Graw Hill publishing; 2012: 1901-15.
4. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115(5):e69-e171
5. Joseph SM, Cedars AM, Mann DL. Acute decompensated heart failure. Tex Heart Inst J. 2010; 37(1):135
6. S Reddy, A. Bahl and KK Talwar. Congestive Heart Failure in Indians: How do we improve diagnosis and management? Indian J Med Res.2010;132(5):549-560

7. Jessup M, Brozena S. Heart failure. 2. *N Engl J Med* 2003; *348* : 2007-18.
8. Kenchaiah S, Narula J, Vasan RS. Risk factors for heart failure. 3. *Med Clin North Am* 2004; *88* : 1145
9. Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure syndromes: current state and framework for future research. *Circulation.* 2005;112(25): 3958–3968
10. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16:e1–194.
11. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur Heart J.2012;33:1787–847.
12. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;119:e391–479.
13. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med.2006;355:251–9.

14. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation. 2009;119:3070–7.
15. Bhuiyan T, Maurer MS. Heart failure with preserved ejection fraction: persistent diagnosis, therapeutic enigma. CurrCardiovasc Risk Rep. 2011;5:440–9.
16. Punnoose LR, Givertz MM, Lewis EF, et al. Heart failure with recovered ejection fraction: a distinct clinical entity. J Card Fail. 2011;17:527–32.
17. Sakai H, Tsutamoto T, Tsutsui T, et al. Serum level of uric acid, partly secreted from the failing heart, is a prognostic marker in patients with congestive heart failure. Circ J;2006;70:1006-1011.
18. Gheorghiade M, Filippatos G, De Luca L, Burnett J: Congestion in acute heart failure syndromes: An essential target of evaluation and treatment. *Am J Med* 2006; 119:S3.
19. Chaudhry SI, Wang Y, Concato J, et al: Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007; 116:1549.

20. Zile MR, Bennett TD, St. John Sutton M, et al: Transition from chronic compensated to acute decompensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008; 118:1433.
21. Fonarow GC, Stough WG, Abraham WT, et al: Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF Registry. *J Am CollCardiol* 2007; 50:768.
22. Yancy CW, Lopatin M, Stevenson LW, et al: Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am CollCardiol* 2006; 47:76.
23. Shah SJ, Gheorghiade M: Heart failure with preserved ejection fraction: Treat now by treating comorbidities. *JAMA* 2008; 300:431.
24. Mebazaa A, Pang PS, Tavares M, et al: The impact of early standard therapy on dyspnoea in patients with acute heart failure: The URGENT-dyspnoea study. *Eur Heart J* 2010; 31:832.

25. Ioachimescu AG, Brennan DM, Hoar BM, et al. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease. Arthritis and Rheumatism; 2008;58(2):623-630.
26. Gheorghiade M, Abraham WT, Albert NM, et al: Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006; 296:2217.
27. Blair JE, Burnett JC, Konstam MA, et al: Prognostic value and changes in renal function in patients admitted with acute heart failure—results from the EVEREST program. *Eur Heart J* 2008; 29(Abstract Suppl):270.
28. Gheorghiade M, Abraham WT, Albert NM, et al: Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: An analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007; 28:980.
29. Gheorghiade M, Rossi JS, Cotts W, et al: Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007; 167:1998.
30. Blair JE, Khan S, Konstam MA, et al: Weight changes after hospitalization for worsening heart failure and subsequent re-hospitalization and mortality in the EVEREST trial. *Eur Heart J* 2009; 30:1666.

31. Wang NC, Maggioni AP, Konstam MA, et al: Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA* 2008; 299:2656.
32. Flaherty JD, Rossi JS, Fonarow GC, et al: Influence of coronary angiography on the utilization of therapies in patients with acute heart failure syndromes: Findings from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2009; 157:1018.
33. Rossi JS, Flaherty JD, Fonarow GC, et al: Influence of coronary artery disease and coronary revascularization status on outcomes in patients with acute heart failure syndromes: A report from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Eur J Heart Fail* 2008; 10:1215.
34. Gheorghiade M, Abraham WT, Albert NM, et al: Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: An analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007; 28:980
35. Konstam MA, Gheorghiade M, Burnett Jr JC, et al: Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA* 2007; 297:1319.

36. Tschuppert Y, Buclin T, Rothuizen LE, et al: Effect of dronedarone on renal function in healthy subjects. *Br J ClinPharmacol* 2007; 64:785
37. Heywood JT, Fonarow GC, Costanzo MR, et al: High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: A report from the ADHERE database. *J Card Fail* 2007; 13:422.
38. Damman K, Navis G, Voors AA, et al: Worsening renal function and prognosis in heart failure: Systematic review and meta-analysis. *J Card Fail* 2007; 13:599.
39. Grayburn PA, Appleton CP, DeMaria AN, et al: BEST Trial Echocardiographic Substudy Investigators: Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: The Beta-blocker Evaluation of Survival Trial (BEST). *J Am CollCardiol* 2005; 45:1064
40. Jones RH, Velazquez EJ, Michler RE, et al: STICH Hypothesis 2 Investigators: Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009; 360:1705.
41. Anand IS, Carson P, Galle E, et al: Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: Results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation* 2009; 119:969.

42. Cleland J, Freemantle N, Ghio S, et al: Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am CollCardiol* 2008; 52:438.
43. Gheorghiade M, Bonow RO: Heart failure: early follow-up after hospitalization for heart failure. *Nat Rev Cardiol* 2010; 7:422.
44. Fonarow GC, Heywood JT, Heidenreich PA, et al: Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: Findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2007; 153:1021
45. Cowrie MR, Jourdain P Maisel AS, et al. Clinical applications of B-type natriuretic peptide (BNP) testing.*Eur Heart J*. Oct 2003;24(19):1710-8.
46. Eugene Braunwald. Biomarkers in Heart Failure. N Engl J Med 2008;358:2148-59.
47. Ziskoven D, Forssmann WG, Holthausen U, Menz G, Addicks K, Rippegater G (1989). "Calcium Calmodulin antagonists Influences the release of Cardiodilatin/ANP from Atrial Cardiocytes". In Kaufmann W, Wambach G. *Handbook Endocrinology of the Heart*. Berlin: Verlag: Springer. pp. 233

48. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. Feb 5 2002;105(5):595-601.
49. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. Jul 18 2002;347(3):161-7.
50. Maisel AS, McCord J, Nowak RM, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *J Am CollCardiol*. Jun 4 2003;41(11):2010-7.
51. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. Feb 12 2004;350(7):655-63.
52. Richards M, Nicholls MG, Espiner EA, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am CollCardiol*. Jan 3 2006;47(1):52-60.
53. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am CollCardiol*2010;56:1071–1078.

54. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494–2502.
55. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F, Maggioni AP, Tavazzi L, Tognoni G, Cohn JN, Latini R. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from two large randomized clinical trials. *Circulation* 2012;125:280–288.
56. Tsutamoto T, Kawahara C, Nishiyama K, Yamaji M, Fujii M, Yamamoto T, Horie M. Prognostic role of highly sensitive cardiac troponin I in patients with systolic heart failure. *Am Heart J* 011;159:63–67.
57. Xue Y, Clopton P, Peacock WF, Maisel AS. Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. *Eur J Heart Fail* 2011;13:37–42.
58. Pascual-Figal DA, Manzano-Fernandez S, Boronat M, Casas T, Garrido IP, Bonaque JC, Pastor-Perez F, Valdes M, Januzzi JL. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. *Eur J Heart Fail* 2011;13:718–725.

59. Adams JE III, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation 1993;88:101– 6.
60. Bodor GS, Porterfield D, Voss EM, Smith S, Apple FS. Cardiac troponin-I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. ClinChem 1995;41:1710 –5.
61. Culleton BF, Larson MG, Kannel WB, Levy D: Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999, 131(1):7-13.
62. Fang J, Alderman MH: Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971– 1992. National Health and Nutrition Examination Survey. *JAMA* 2000, 283(18):2404-2410.
63. Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka HM, Lakka TA, Salonen JT: Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004, 164(14):1546-1551.
64. Freedman DS, Williamson DF, Gunter EW, Byers T: Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow up Study. *Am J Epidemiol* 1995, 141:637-644.
65. Alderman MH: Uric acid and cardiovascular risk. *Curr Opin Pharmacol* 2002, 2(2):126-130.

66. Verdecchia P, Schillaci G, Reboldi GP, Santeusanio F, Porcellati C, Brunetti P: Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. *Hypertension* 2000, 36:1072-1078.

67. Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U: Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. *Epidemiology* 1999, 10:391-397.

68. Brand FN, McGee DL, Kannel WB, Stokes J III, Castelli WP: Hyperuricemia as a risk factor of coronary heart disease: the Framingham study. *Am J Epidemiol* 1985, 121:11-18.

69. Wannamethee SG, Shaper AG, Whincup PH: Serum urate and the risk of major coronary heart disease events. *Heart* 1997, 78(2):147- 153. (Part of the cluster not independent)

70. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW, Applegate WB: Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000, 18(8):1149-1154.

71. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003, 41(6):1183-1190.
72. Alderman M, Aiyer KJ: Uric acid: role in cardiovascular disease and effects of losartan. *Curr Med Res Opin* 2004, 20(3):369-379.
73. Wang JG, Staessen JA, Fagard RH, Birkenhager WH, Gong L, Liu L: Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 2001, 37(4):1069-1074
74. M.R. Hayden, S.C.Tyagi. *Nutrition & Metabolism* 2004, 1:10 doi:10.1186/1743-7075-1-10
75. Luft FC "Hypertension as a complex genetic trait" *Seminar in Nephrology*, 2002 22:115.
76. Kylin E: Studien ueber das Hypertonie-Hyperglyka "mie- Hyperurika" miesyndrom. *Zentralblatt fuer Innere Medizin* 1923, 44:105-127.
77. Robert L. Wortmann "Disorders of Purine and Pyrimidine Metabolism" *Harrison's Principles of Internal Medicine* 16th edition, Mc-Gram Hill, 2309.
78. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988, 37(12):1595-1607.

79. Zavaroni I, Mazza S, Fantuzzi M, Dall'Aglio E, Bonora E, Delsignore R, Passeri M, Reaven GM: Changes in insulin and lipid metabolism in males with asymptomatic hyperuricaemia. *J Intern Med* 1993, 234(1):25-30.
80. Hayden MR, Tyagi SC: Intimal redox stress: Accelerated atherosclerosis in metabolic syndrome and type 2 diabetes mellitus. Atherosclerosis. *Cardiovasc Diabetol* 2002, 1(1):3.
81. Griendling KK, Sorescu D, Ushio-Fukai M: NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000, 86:494- 501.
82. Hayden MR: Global risk reduction of reactive oxygen species in metabolic syndrome, type 2 diabetes mellitus, and atherosclerosis. *Medical Hypotheses and Research* 2004, 1(2–3):171-185.
83. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH: Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966, 275(9): 457-464
84. Lin KC, Tsao HM, Chen CH, Chou P: Hypertension was the major risk factor leading to development of cardiovascular diseases among men with hyperuricemia. *J Rheumatol* 2004, 31(6):1152- 1158.
85. Wu X, Wakamiya M, Vaishnav S, Geske R, Montgomery C Jr, Jones P, Bradley A, Caskey CT: Hyperuricemia and urate nephropathy in urate oxidase-deficient mice. *Proc Natl Acad Sci U S A* 1994, 91(2):742-746.

86. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001, 38(5):1101-1106.

87. Bedir A, Topbas M, Tanyeri F, Alvur M, Arik N: Leptin might be a regulator of serum uric acid concentrations in humans. *Jpn Heart J* 2003, 44(4):527-536.

88. Conen D, Wietlisbach V, Bovet P, Shamlaye C, Riesen W, Paccaud F, Burnier M: Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health* 2004, 4(1):9.

89. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatoryi V, Tosi F, Travia D, Zenti MG, Branzi P, Santi L, Muggeo M: Relationship of uric acid concentration to cardiovascular risk factors in young men. The role of obesity and central fat distribution, The Verona Young Men Atherosclerosis Risk Factors Study. *Int J Obes Relat Metab Disord* 1996, 20:975-980.

90. Williamson JR, Kilo C, Ido Y: The role of cytosolic reductive stress in oxidant formation and diabetic complications. *Diabetes Res Clin Pract* 1999, 45:81-82.

91. Aronson D, Rayfield EJ: How hyperglycemia promotes atherosclerosis: molecular mechanisms. *Cardiovasc Diabetol* 2002, 1(1):1.
92. Santos CX, Anjos EI, Augusto O: Uric acid oxidation by peroxynitrite: multiple reactions, free radical formation, and amplification of lipid oxidation. *Arch Biochem Biophys* 1999, 372(2):285-294.
93. Abuja PM: Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. *FEBS Lett* 1999, 446(2–3):305-308.
94. Hayden MR, Tyagi SC: Homocysteine and reactive oxygen species in metabolic syndrome, type 2 diabetes mellitus, and atherosclerosis: The pleiotropic effects of folate supplementation. *Nutr J* 2004, 3(1):4.
95. Evers S, Koch HG, Grotemeyer KH, Lange B, Deufel T, Ringelstein EB: Features, symptoms, and neurophysiological findings in stroke associated with hyperhomocysteinemia. *Arch Neurol* 1997, 54(10):1276-1282.
96. Hong YS, Lee MJ, Kim KH, Lee SH, Lee YH, Kim BG, Jeong B,Yoon HR, Nishio H, Kim JY: The C677 mutation in methylene tetrahydrofolate reductase gene: correlation with uric acid and cardiovascular risk factors in elderly Korean men. *J Korean Med Sci* 2004, 19(2):209-213.
97. Insulin Resistance – Insulin Action and its disturbance in Disease Sudhesh Kumar, Stephen O'Rahilly.

98. O' Rahilly, S., Hattersley, A and Gray, H. (1994) Insulin Resistance as the major cause of impaired glucose tolerance a self fulfilling prophesy? Lancet 344, 585-589

99. Venkatesan, A.M., Dunaif.A., and Corbould, A. (2001) Insulin Resistance and Polycystic ovary syndrome: progress and paradoxes. Recent Prog Horm Res. 56, 295-308.

100. Donohue, W. and Uchida, I (1954) Leprechaunism: a euphemism for a rare familial disorder. J. Pediatr 45, 505-519.

101. Anker SD, Doehner W, Rauchhaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003; 107:1991-1997.

102. Kittleson MM, St John ME, Bead V, et al. Increases levelslevels of uric acid predict haemodynamic compromise in patients with heart failure independently of B-type natriuretic peptide levels. Heart. 2007; 93:365-367.

103. Pascual-Figal DA, Hurtado-Martinez JA, Redondo B, et al. Hyperuricaemia and long-term outcome after hospital discharge in acute heart failure patients. European Journal of Heart Failure. 2007; 9: 518–524

104. Levya F, Anker S, Swan JW, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *European Heart Journal.*1997; 18: 858-865

105. Hare JM, Johnson RJ. Uric Acid Predicts Clinical Outcomes in Heart Failure Insights Regarding the Role of Xanthine Oxidase and Uric Acid in Disease Pathophysiology. *Circulation.* 2003;107:1951-1953

106. Kroll K, Bukowski TP, Schwartz LM, et al. Capillary endothelial transport of uric acid in guinea pig heart. AM J Physiol; 1992;262:H420-H431.

107. Castelli P, Condemi AM, Brambillasca C, et al. Improvement of cardiac function by allopurinol in patients undergoing cardiac surgery. J Cardiovasc Pharmacolol; 1995;25: 119-125

108. Kogure K, Ishizaki M, Nemoto M, et al. Evaluation of serum uric acid changes in different forms of hepatic vascular inflow occlusion in human liver surgeries. Life Sci; 1999; 64: 305-318

109. Mathru M, Dries DJ, Barnes L, et al. Torniquet-induced exsanguinous in patients requiring lower limb surgery. An ischemia-reperfusion model of oxidant and antioxidant metabolism. Anaesthesiology; 1996;84:14-22.

110. Traut EF, Knight AA, Szanto PM, et al. Specific vascular changes in gout. JAMA. 1954;156:591-593.

111. Tziomalos K, Hare JM. Role of xanthine oxidoreductase in cardiac nitroso-redox imbalance. Front Biosci; 2009;14:237.

112. Predergast BD, Sagach VF, Shah AM, et al. Basal release of nitric oxide augments the Frank-Starling response in the isolated heart. Circulation;1997;96:1320-29.

113. Kojimo S, Sakamoto T, Ishihara M, et al. Prognostic usefulness of serum uric acid after acute myocardial infarction (Japanese Acute Coronary Syndrome Study). Am J Cardiol;2005;96:489-95.

114. Bickel C, Rupprecht HJ, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary heart disease. Am J Cardiol;2002;89:12-17.

115. Car S, Trkulja V. Higher serum uric acid on admission is associated with higher short-term mortality and poorer long-term survival after myocardial infarction: retrospective prognostic study. Croat Med J; 2009;50:559-66.

116. Hoieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int; 2004;65:1041-1049.

117. Athyros VG, Elisaf M, Papageorgiou AA, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study. Am J Kidney Dis; 2004;43:589-599.

ANNEXURES

PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION

S.No: Uric Acid: mg/dl

Name : Occupation:

Age / Sex: Address:

Weight: BMI:

DOA: DOD: Phone No:

ETIOLOGICAL DIAGNOSIS :

Ischaemic heart disease ☐ Rheumatic heart disease ☐

Congenital heart disease ☐ Others ☐

RISK FACTORS:

SHT ☐ Smoking ☐ Dyslipidemia ☐

DM ☐ Alcohol ☐ Others ☐

CLINICAL FEATURES:

NYHA Functional class: I /II/ III / IV SBP:

Dyspnoea ☐ DBP:

Edema ☐ Pulse Rate:

Cough ☐ Apex:

Chest Pain ☐ JVP:

Palpitation ☐ Acute / chronic :

ELECTROCARDIOGRAM:

Ischemic changes ☐

LAE ☐

LVH ☐

Arrhythmias ☐

QRS Duration QRS >120ms ☐

QRS < 120ms ☐

ECHOCARDIOGRAM:

LVEF % :

RWMA ☐

Valvular Heart Diseases

MS ☐ AS ☐

MR ☐ AR ☐

Others ☐

X-RAY CHEST:

CTR :

Cardiomegaly ☐

Pulmonary Edema ☐

TREATMENT:

Required Inotropes

Yes ☐ **No** ☐

PROGNOSIS:

Mortality

< 1 day ☐

1-7 days ☐

7-30 days ☐

Rehospitalisation < 30 days

Yes ☐

No ☐

MASTER CHART

S.N0	Name	Age	Age Gr	Sex	UA	UA Gr	EF	EF Gr	DM	SHT	Alcoh	Smok	Dys	Eti	A/C	NYHA	Mort	Reh	Ino	QRS
1	ponnusamy	55	5	M	8.9	4	24	4	1	1	1	1	1	1	2	3	1	1	1	1
2	raju	50	5	M	7.6	3	36	3	1	2	1	1	1	1	2	3	2	2	2	2
3	lakshmi	54	5	F	8.8	4	43	2	1	1	2	2	1	1	2	3	2	2	2	1
4	sundaram	57	5	M	9.8	5	28	4	1	1	1	1	1	1	1	4	1	1	1	1
5	rajamani	44	4	F	9	5	30	3	1	1	2	2	1	1	1	3	2	2	1	1
6	sabarathnam	76	7	M	6	1	42	2	2	2	2	1	2	1	2	2	2	2	2	2
7	subramani	44	4	M	7.4	3	44	2	1	2	2	1	2	1	2	3	2	2	2	1
8	sarasu	36	3	F	8.4	4	32	3	2	2	2	2	2	2	2	3	2	2	1	2
9	arunachalam	47	4	M	8.2	4	31	3	1	1	1	2	1	1	2	3	2	2	1	1
10	eswaran	62	6	M	5.9	1	56	1	1	1	2	1	1	3	2	2	2	2	2	2
11	saraswat	80	8	F	9	5	22	4	1	1	2	2	1	1	2	3	1	2	1	1
12	murugan	55	5	M	5.4	1	46	2	2	2	2	2	2	1	2	3	2	2	2	2
13	kaliammal	27	2	F	7.8	3	34	3	2	2	2	2	2	2	1	3	2	2	2	2
14	rajesh	32	3	M	8.8	4	29	4	2	2	2	1	2	2	1	4	2	2	1	2
15	Parvathi	56	5	F	8.1	4	44	2	2	1	2	2	2	4	2	3	2	2	2	2
16	rajan	65	6	M	7.8	3	36	3	2	2	1	1	1	1	2	3	2	2	2	2
17	amudha	28	2	F	9.1	5	34	3	2	2	2	2	2	2	1	4	2	2	2	2
18	madesh	48	4	M	9.4	5	28	4	1	1	1	1	1	1	1	4	2	1	1	1
19	arumugam	36	3	M	7.9	3	36	3	2	2	2	1	2	2	2	3	2	2	2	2
20	selvi	28	2	F	9.2	5	30	3	2	2	2	2	2	2	1	4	2	2	1	2
21	Tamilselvan	34	3	M	8.1	4	32	3	2	2	1	1	2	2	1	4	2	2	2	2
22	Jasmine	30	3	F	8.6	4	36	3	2	2	2	2	2	2	2	3	2	2	2	2
23	akbar ali	67	6	M	6	1	58	1	1	1	2	1	1	3	2	4	2	2	2	2
24	Jeyammal	62	6	F	8.8	4	31	3	1	1	2	2	1	1	1	4	1	1	1	2
25	nagaraj	65	6	M	9.4	5	36	3	1	1	1	1	1	1	1	4	1	1	2	1
26	sundari	48	4	F	7.8	3	42	2	2	2	2	2	1	1	2	3	2	2	2	1
27	samsudeen	63	6	M	7.4	3	46	2	2	2	1	1	2	4	2	3	2	2	2	2
28	lakshmi	39	3	F	8.8	4	32	3	2	2	2	2	2	2	1	4	2	1	1	2

29	kuppusamy	74	7	M	6.8	2	45	2	2	2	2	1	1	1	2	2	2	2	2	2
30	rukmani	50	5	F	7	2	42	2	2	2	2	2	1	1	2	3	2	2	2	2
31	shanmugam	75	7	M	5.8	1	46	2	2	2	1	1	2	1	2	2	2	2	2	2
32	valli	32	3	F	8.6	4	32	3	2	2	2	2	2	2	1	3	2	2	1	2
33	jayraj	56	5	M	8.2	4	42	2	1	1	1	1	1	4	2	3	2	2	2	2
34	Ramani	52	5	F	7.5	3	46	2	2	2	2	2	2	4	2	3	2	2	2	2
35	jaykumar	37	3	M	9.2	5	27	4	2	2	1	1	2	2	1	4	2	2	1	2
36	sukumar	50	5	M	9	5	32	3	1	1	1	1	1	1	1	4	1	1	1	1
37	kanagavalli	56	5	F	8.1	4	41	2	1	1	2	2	1	1	2	3	2	1	2	1
38	ramasamy	72	7	M	7.2	3	46	2	2	2	1	1	1	1	2	3	2	2	2	1
39	saraswathi	60	6	F	7.6	3	42	2	2	1	2	2	2	4	2	3	2	2	2	2
40	kumar	34	3	M	8.6	4	32	3	2	2	1	1	2	2	1	4	2	2	1	2
41	mariammal	62	6	F	6.2	2	46	2	2	2	2	2	2	4	2	3	2	2	2	2
42	rathnam	64	6	M	7.6	3	44	2	2	2	1	1	1	1	2	3	2	2	2	2
43	palanisamy	62	6	M	6.8	2	37	3	1	2	1	1	2	1	2	3	2	2	2	2
44	saravanan	48	4	M	5.9	1	48	2	2	2	2	1	2	1	2	2	2	2	2	2
45	jayakumari	53	5	F	9.2	5	29	4	1	1	2	2	1	1	2	3	1	2	1	1
46	kadhir	40	4	M	6.4	2	48	2	2	2	1	1	2	1	2	2	2	2	2	2
47	rasamma	80	8	F	7.8	3	38	3	2	1	2	2	1	1	2	3	2	2	2	2
48	velu	30	3	M	9.1	5	28	4	2	2	2	1	2	2	1	4	2	2	1	2
49	kadhiresan	35	3	M	8.8	4	34	3	2	2	2	1	2	2	1	4	2	2	2	2
50	rakkayi	56	5	F	7.2	3	45	2	2	2	2	2	2	1	2	3	2	2	2	2
51	Muthumani	45	4	M	8.2	4	34	3	1	1	1	1	1	1	2	3	2	2	2	2
52	latha	56	5	F	5.6	1	47	2	2	2	2	2	2	1	2	2	2	2	2	2
53	Manikandan	32	3	M	9	5	35	3	2	2	2	2	2	2	1	4	2	2	2	2
54	Sundareswari	60	6	F	8	4	42	2	1	1	2	2	1	1	2	3	2	2	2	2
55	Rajamanikam	52	5	M	9.4	5	27	4	1	1	1	1	1	1	1	4	1	2	1	1
56	Boomithai	45	4	F	5.4	1	48	2	2	2	2	2	2	1	2	2	2	2	2	2
57	Sachidanandam	55	5	M	7.6	3	36	3	2	2	2	2	2	2	1	4	2	2	2	2
58	Vijay	32	3	M	8.4	4	34	3	1	1	2	2	1	1	2	3	2	2	2	2

59	Rajathi	33	3	F	8.4	4	36	3	1	1	1	1	1	1	1	4	1	2	1	1
60	Kuppusamy	68	6	M	7.2	3	42	2	2	2	1	1	1	1	2	3	2	2	2	2
61	Rangaraj	65	6	M	5.4	1	46	2	2	2	2	2	2	1	2	2	2	2	2	2
62	Lakshmanan	45	4	M	5.9	1	54	1	1	1	2	2	1	3	2	1	2	2	2	2
63	Raja	44	4	M	5.6	1	48	2	2	2	2	2	1	4	1	2	2	2	2	2
64	Munusamy	75	7	M	5.8	1	54	1	1	1	2	1	1	3	2	1	2	2	2	2
65	Kanaga	60	4	F	8.6	4	34	3	1	1	2	2	1	1	1	4	1	2	1	1
66	Ganasan	55	5	M	7	2	46	2	2	2	1	1	2	1	2	2	2	2	2	2
67	Malliga	60	6	F	8.8	4	39	3	1	1	2	2	1	1	2	3	2	2	2	1
68	madesh	45	4	M	5.4	1	52	1	1	1	2	2	2	3	2	1	2	2	2	2
69	Asairani	48	4	F	9.3	5	32	3	1	1	2	2	1	2	1	3	2	2	1	2
70	Sanjeevan	60	6	M	6	1	56	1	1	1	1	2	1	3	2	1	2	2	2	2
71	Booma	47	4	F	9.2	5	32	3	1	1	2	2	1	1	1	4	2	2	1	1
72	Nagalaxmi	55	5	F	8.1	4	42	2	1	1	2	2	1	1	2	3	2	2	2	1
73	Udayakumar	53	5	M	6.6	2	48	2	2	2	1	1	2	4	2	3	2	2	2	2
74	Kumari	44	4	F	8.1	4	32	3	2	1	2	2	1	2	1	4	2	2	1	2
75	Surendran	57	5	M	5.4	1	52	1	2	2	1	1	2	1	2	2	2	2	2	2
76	Krishnaveni	60	6	F	7.5	3	42	2	2	2	2	2	1	1	2	3	2	2	2	2
77	Marudhu	50	5	M	8.6	4	34	3	1	1	1	1	1	1	1	4	1	1	2	1
78	Malleswari	60	6	F	5.2	1	54	1	1	1	2	2	2	3	2	3	2	2	2	2
79	Dandapani	40	4	M	7	2	46	2	1	1	1	1	1	1	2	3	2	2	2	2
80	Kathiresan	40	4	M	5.8	1	48	2	2	2	1	2	2	1	2	2	2	2	2	2
81	Krishnan	80	8	M	7.4	3	33	3	2	2	1	1	1	1	2	3	2	2	1	2
82	Anandhi	36	3	F	8	4	32	3	2	2	2	2	2	2	1	4	2	1	1	2
83	Arivalagan	44	4	M	8.6	4	32	3	1	1	1	1	1	1	1	4	2	1	1	1
84	Arokiamary	28	2	F	8.8	4	28	4	2	2	2	2	2	2	1	4	2	2	1	2
85	Venkatachalam	64	6	M	6.8	2	46	2	1	1	1	1	2	1	2	3	2	2	2	2
86	Palani	70	7	M	7	3	48	2	2	1	1	1	2	1	2	3	2	2	2	2
87	Muthusamy	61	6	M	5.8	1	58	1	1	1	2	2	1	3	2	3	2	2	2	2
88	Devan	48	4	M	7.4	3	42	2	2	1	1	1	1	1	2	3	2	2	2	2

89	Pughalendhi	62	6	M	8.8	4	34	3	1	1	1	1	1	1	1	4	1	2	2	1
90	Das	55	5	M	7.4	3	41	2	1	1	1	1	1	1	2	3	2	2	2	2
91	Asokan	33	3	M	9	5	32	3	2	2	2	2	2	2	1	4	2	1	2	2
92	Sakthi	46	4	F	5.4	1	42	2	1	2	2	2	2	1	2	1	2	2	2	2
93	Sharma	60	6	M	9	5	28	4	1	1	1	1	1	1	1	4	1	2	1	2
94	Suganthi	35	3	F	8.2	4	36	3	2	2	2	2	2	2	1	3	2	1	2	2
95	Karuppasamy	65	6	M	8.6	4	41	2	1	1	1	1	1	1	2	3	2	2	2	2
96	Sadagopan	47	4	M	7.6	3	44	2	2	2	1	1	1	1	2	3	2	2	2	1
97	Subramani	73	7	M	7.4	3	36	3	1	1	1	2	1	1	2	3	2	2	2	2
98	Veeradas	50	5	M	7.2	3	42	2	2	2	1	2	1	1	2	2	2	2	2	2
99	Jaffer	60	6	M	6.2	2	48	2	2	2	2	2	2	1	2	1	2	2	2	2
100	Veni	40	4	F	8	4	32	3	2	1	2	2	2	2	1	3	2	2	1	2

KEY TO MASTER CHART

S.No	-	Serial number
Age Gr	-	Age Grade
UA	-	Uric Acid
UA Gr	-	Uric Acid Grade
EF	-	Ejection Fraction
EF Gr	-	Ejection Fraction Grade
DM	-	Diabetes Mellitus
SHT	-	Systemic Hypertension
Alcoh	-	Alcohol Intake
Smok	-	Smoker
Dys	-	Dyslipidemia
A	-	Acute (1)
C	-	Chronic (2)
NYHA	-	New York Heart Association Functional class for heart failure
Ino	-	Inotropes required
Reh	-	Rehospitalisation within 30 days
QRS	-	QRS Duration > 120 msec
1	-	Yes
2	-	No
M	-	Male
F	-	Female

INFORMED CONSENT

DEPARTMENT OF GENERAL MEDICINE

Coimbatore Medical College,

Coimbatore

Principal investigator	:	Dr. Suresh.S
Research guide	:	Dr.S.Manoharan , M.D.
Organisation	:	Department of General Medicine
Informed consent	:	I have been invited to participate in research

project titled

'PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN CONGESTIVE CARDIAC FAILURE AND ITS CORRELATION WITH EJECTION FRACTION'

I understand, it will be answering a set of questionnaire, undergo physical examination, investigations and appropriate treatment.

I also give consent to utilize my personal details for study purpose and can be contacted if necessary.

I am aware that I have the right to withdraw at any time which will not affect my medical care.

Name of the participant:

Signature:

Date:

xggjy;gotk;

bgah; :

ghypdk; : taJ:

Kfthp :

muRnfhit kUj;Jtf;fy;Y}hpapy;bghJ kUj;Jtj;Jiwapy;gl;l nkwgogg[gapYk; khztH;nkwbfhs;Sk; "**,ja brayHggpy; ,ujj a(hpf; mkpy';fspd; neha; gwwpa Kdpdwptggpd; Kf;fpaj;Jt';fSk; kwWk; ,ujj btspnawwj; jpwDld; mjDila bjhlhgk;**" Fwpj;j Ma;tpy;bra;Kiw kwWk;midj;J tptu';fisak;nfl;Lf;bfhz;L vdJ renjf';fis bjspthgLj;jpf;bfhz;nld;vdgij bjhptpj;Jf; bfhs;fpnwd;

ehd;,e;j Ma;tpy;KG rk;kjj;JlDk/Ra rpe;jida[lDk;fye;J bfhs;s rk;kjpf;fpnwd;

,e;j Ma;tpy;vdDila midj;J tpgu';fs;ghJfhf;fggLtJld; ,jd; Kotfs; Ma;tpjHpy; btspaplggLtjpy; Mlnrgid ,y;iy vdgij bjhptpj;Jf;bfhs;fpnwd; ve;j neuj;jpYk; ,e;j Ma;tpypUe;J ehd;tpyfpf;bfhs;s vdf;F chpik czL vdgijak;mwpntd;

,lk;: ifbahggk;/nuif

ehs;: